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Alpha Cognition, Inc. (ACOGF - OTC)

Alpha-1062: Prodrug Pole Position

Based on our DCF model and a 15% discount rate, Alpha Cognition is valued at approximately $2.75 per share. Our model applies a 62% probability of ultimate approval and commercialization of Alpha-1062. The model includes contributions from North America, Asia Pacific and other developed markets.

Current Price (3/4/2022)	$0.77
Valuation	**$2.75**

INITIATION

Alpha Cognition is developing Alpha-1062, a prodrug of galantamine that is in Ph3 development for mild to moderate AD. Additional pre-clinical work for Alpha-1062 is being conducted in mild TBI. The company is also advancing a preclinical progranulin gene therapy program for ALS.

With few advances in decades, AD represents a material unmet need. While some drugs exist to treat the symptoms of AD, side effects may limit use. To address GI-related side effects and optimize dose, a prodrug of previously approved galantamine has been developed which avoids active drug interaction in the intestine. Exploratory studies have demonstrated an improved GI side effect profile and combined with other findings showing stable cognition, improved mortality and lower burden on caregivers, the drug makes a compelling argument for long-term use in AD patients. The new compound is expected to boost compliance in patients, in order for galantamine's benefits to be realized.

Alpha-1062 should present top line results in 2Q:22 for AD, with an NDA filing in 3Q:22 submitted via the 505(b)(2) regulatory pathway. Other early stage programs will target readouts for mild TBI and progranulin in 2022. Formulation development is also underway for a combination approach for Alpha-1062 and memantine to treat moderate to severe AD.

SUMMARY DATA

52-Week High	**1.80**
52-Week Low	**0.68**
One-Year Return (%)	**4.0**
Beta	**N/A**
Average Daily Volume (sh)	**14,319**
Shares Outstanding (mil)	**60.6**
Market Capitalization ($mil)	**46.7**
Short Interest Ratio (days)	**0.15**
Institutional Ownership (%)	**0.2**
Insider Ownership (%)	**23.8**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2022 Estimate	**N/A**
P/E using 2023 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**Above Average**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue

(In millions of USD)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2020	$0.0 A	$0.0 A	$0.0 A	$0.0 A	$0.0 A
2021	$0.0 A	$0.0 A	$0.0 A	$0.0 E	$0.0 E
2022					$0.0 E
2023					$0.0 E

Earnings per Share

	Q1	Q2	Q3	Q4	Year
2020	-$0.02 A	-$0.04 A	-$0.07 A	-$0.00 A	-$0.13 A
2021	-$0.28 A	$0.00 A	-$0.09 A	-$0.06 E	-$0.41 E
2022					-$0.20 E
2023					-$0.14 E

INITIATION

Alzheimer's Disease (AD) was the seventh most common cause of death in the United States in 2020 and the fastest growing cause in the top ten over both 10 and 20 year periods. Prevalence of AD is highly associated with age, making it a critical challenge in all regions with a quickly aging population particularly Europe and China. In contrast to other leading causes of death, a clinically-proven disease modifying therapy has eluded medicine; nevertheless, there are symptomatic treatments available for AD and new formulations may improve their safety and efficacy. The two existing classes of symptomatic treatment include acetylcholinesterase inhibitors (AChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists. A member of the former class, galantamine, has been clinically shown to reduce severe dementia, maintain cognition and reduce caregiver burden; however, many patients stop taking the drug due to side effects including nausea, vomiting, diarrhea, weight loss and dizziness. Recognizing this shortcoming, Alpha Cognition Incorporated (OTC: ACOGF) has developed a prodrug formulation of galantamine designated Alpha-1062 which may be able to sidestep unwanted side effects but still confer the drug's benefits.

Alpha-1062, is a prodrug of galantamine which avoids many of the unconjugated version's gastrointestinal (GI) issues. This formulation adds an ester to the base molecule to create a prodrug which allows an inactive form of the drug to be absorbed in the small intestine. Via liver metabolism, Alpha-1062 converts into active galantamine and travels to the brain where it imparts its neuroprotective effect by inhibiting the enzymatic breakdown of acetylcholine (ACh) and enhancing the sensitivity of nicotinic acetylcholine receptors (nAChRs).

There are over six million individuals with AD in the United States and more than 30 million globally[1] presenting an immense population that has few treatment alternatives. Based on a 2017 Medicare cohort study,[2] about 56% of AD patients were prescribed anti-dementia drugs, suggesting an addressable market of almost 3.5 million in the US. As the discontinuation rate is high for AChEIs due to side effects, improvements in this limitation could materially benefit the addressable market and lead to a share shift towards Alpha-1062. Combining better compliance with the long-term advantages of galantamine may provide material cognition and cost benefits to patients and reduce the burden for caregivers.

Alpha Cognition's predecessor, Neurodyn, was founded in 2000 to study drug opportunities in neurology. This led to the acquisition of Alpha-1062 in 2008 which was shown to provide a material improvement in GI side effects. After several years of continued product development and refinement of regulatory strategy, Alpha Cognition was formed through a reverse merger in 2020. With $4.7 million in cash on the balance sheet augmented by a $10+ million post-quarter public offering and a clear path forward to approval using the lower-risk 505(b)(2) pathway, the company represents an attractive investment opportunity. If successful in its lead monotherapy program for AD, the company offers other programs in development.

Alpha Cognition is expanding its efforts beyond AD monotherapy using AChEIs in other areas of the neurodegenerative field. The company is in preclinical development with other programs including a combination approach for Alpha-1062 with memantine for AD and Alpha-1062 for mild traumatic brain injury (mTBI). The fourth program is developing a progranulin gene therapy for amyotrophic lateral sclerosis (ALS), designated Alpha-0602.

In this report we provide a review of AD, its prevalence, death rate relative to other common diseases and economic impact. We then shift towards other aspects of the disease including its etiology, diagnosis and the mechanism behind neurotransmission which are key to understanding galantamine's mechanism of action. A review of other products approved for AD is provided including several in development. Alpha Cognition's 505(b)(2) pathway to approval is also described. Following this background, we introduce Alpha-1062, providing the history behind the drug, its mechanism of action, most common side effects and observed benefits as promulgated in a broad spectrum of clinical research. Our report then moves on to a short description of the other programs in the company's portfolio. The following sections discuss Alpha Cognition's intellectual property rights and patents and provide a financial and operational review of the company including upcoming milestones and introduce management. Risks to the company are highlighted along with a summary of peers and competitors and their market size. We complete our review with a detailed discussion of our assumptions behind the company's valuation. The result of our valuation work generates a price target of $2.75 per share.

[1] The WHO estimates that there are more than 55 million living with dementia in 2021. With 60-70% of dementia cases considered AD, this suggests from 33 to 39 million are afflicted with AD.
[2] Koller, D, *et al.* Treatment Patterns with Anti-Dementia Drugs in the United States: Medicare Cohort Study. J Am Geriatr Soc. 2017

Key reasons to own Alpha Cognition shares:

- **Attractive indications with material unmet need**
  - **Alzheimer's Disease (AD)**
  - **Traumatic Brain Injury (TBI)**
  - **Amyotrophic Lateral Sclerosis (ALS)**
- **Galantamine is the active metabolite of Alpha-1062**
  - **Can significantly slow AD & reduce all-cause mortality**
  - **Shorter titration schedule providing faster onset of action**
  - **Differentiating beneficial effects on nicotinic receptor**
  - **Addresses GI side effects through prodrug formulation**
  - **Low rates of insomnia vs. other AChEIs**
  - **Considered a new chemical entity (NCE)**
- **Modulates multiple receptors for synergistic effect**
  - **Binding to AChE allows for greater amounts of ACh to persist**
  - **Binding to nAChR enhances the signal from ACh**
- **505(b)(2) Regulatory Pathway for Alpha-1062**
  - **Abbreviated Route to Approval**
  - **Lower Cost**
  - **Allows use of innovator safety and efficacy information**
- **Progranulin gene therapy program**
  - **Pursuing indication in amyotrophic lateral sclerosis (ALS)**
  - **Mammal data available in 1Q:22**

Disease

Alzheimer's Disease

Alzheimer's Disease (AD) is a neurodegenerative condition which affects over six million Americans[3] and over 30 million people worldwide.[4] Due to the faster growth of older population cohorts and the higher prevalence of Alzheimer's in those over 65, numbers of those diagnosed with AD are expected to almost double and triple by 2030 and 2050 respectively. AD is distinguished among the top ten causes of death as it is the fastest growing since 2000.[5] Our review of 2020 CDC data found that deaths resulting from heart disease, cancer and cerebrovascular disease increased 17%, 5% and 24% over the last decade compared with Alzheimer's deaths which rose 61%.

Exhibit I – Leading Causes of Death by Number of Fatalities: 2000 – 2020[6]

Cause of Death	10 yr gro	20 yr gro	2020	2019	2018	2017	2016	2015	2014	2013	2012	2011	2010	2000
Heart	17%	-2%	696,962	659,041	655,381	647,457	635,260	633,842	614,348	611,105	599,711	596,577	597,689	710,760
Cancer	5%	9%	602,350	599,601	599,274	599,108	598,038	595,930	591,700	584,881	582,623	576,691	574,743	553,091
COVID-19			350,831											
Accidents	66%	105%	200,955	173,040	167,127	169,936	161,374	146,571	135,928	130,557	127,792	126,438	120,859	97,900
Cerebrovascular	24%	-4%	160,264	150,005	147,810	146,383	142,142	140,323	133,103	128,978	128,546	128,932	129,476	167,661
Respiratory	11%	25%	152,657	156,979	159,486	160,201	154,596	155,041	147,101	149,205	143,489	142,943	138,080	122,009
Alzheimer's (AD)	61%	171%	134,242	121,499	122,019	121,404	116,103	110,561	93,541	84,767	83,637	84,974	83,494	49,558
Diabetes	48%	47%	102,188	87,647	84,946	83,564	80,058	79,535	76,488	75,578	73,932	73,831	69,071	69,301
Flu/Pneumonia	7%	-18%	53,544	49,783	59,120	55,672	51,537	57,062	55,227	56,979	50,636	53,826	50,097	65,313
Nephritis	4%	41%	52,547	51,565	51,386	50,633	50,046	49,959	48,146	47,112	45,622	45,591	50,476	37,251
Liver	62%	94%	51,642	44,358	42,838	41,743	40,545	40,326	38,170	36,427	34,979	33,642	31,903	26,552
Suicide	73%	57%	45,979	47,511	48,344	47,173	44,965	44,193	42,826	41,149	40,600	39,518	26,634	29,350
Hypertension	57%	132%	41,907	36,524	35,835	35,316	33,246	32,200	30,221	30,770	29,115	27,853	26,634	18,073
Parkinson's (PD)	83%		40,284	35,311	33,829	31,963	29,697	27,972	26,150	25,196	23,818	23,111	22,032	
Septicemia	15%	28%	40,050	38,431	40,718	40,922	40,613	40,773	38,940	38,156	35,842	35,748	34,812	31,224

AD is named after Alois Alzheimer who made the first clinical observations of the disease between 1901 and 1906. He observed a 50-year old female patient who experienced memory loss, paranoia and psychological changes. After the patient's death, an autopsy was performed on her brain which found shrinkage in and around nerve cells and abnormal deposits that were later identified as Aβ plaques and neurofibrillary tangles.

According to the CDC,[7] AD is the 7th leading cause of death in the United States in 2020, after chronic lower respiratory diseases and before diabetes. While there are over 6 million individuals in the US diagnosed with AD, many more are in earlier stages of the disease called mild cognitive impairment (MCI). MCI is seen as a precursor to AD and is measurable by a change in thinking abilities. A person with MCI can carry on normal everyday tasks, but does show some signs of impairment in sensitive testing.

More women than men suffer from AD. According to data cited by the Alzheimer's Association report, almost two thirds of Americans with AD are women. Research is not conclusive on why this difference exists and some attribute it to longer life spans while others have suggested biological or genetic variations. Along racial lines, African-Americans and Hispanics are more likely to suffer from dementia. Research has attributed health, lifestyle and socioeconomic elements as well as higher prevalence of associated health conditions such as cardiovascular disease to the difference.

Deaths from AD are underreported due to other conditions being cited on death certificates. Dementia can cause problems with mobility, nutrition and self-care that can lead to pneumonia, which is frequently cited as the main reason. AD is unique among the most common forms of death in the older population in its increasing prevalence. While improvements in health care have led to decreases in the rate of cancer, heart disease and stroke death, AD

[3] Alzheimer's Association Facts and Figures. Accessed February 2022.
[4] Our adjustments to WHO estimates.
[5] Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying Cause of Death 1999-2020 on CDC WONDER Online Database. Accessed at http://wonder.cdc.gov/ucd-icd10.html
[6] Center for Disease Control and Prevention, National Center for Health Statistics. Compiled by Zacks' Analysts
[7] Center for Disease Control and Prevention, National Center for Health Statistics. Accessed at http://wonder.cdc.gov/ucd-icd10.html

has moved in the other direction and increased substantially. This disturbing trend highlights the need to make progress in this difficult therapeutic area.

The economic burden from AD is immense. Some individuals suffer for decades with the disease and require substantial amounts of care either from family members or nursing homes. Statistics from a variety of sources peg the annual cost of care at over $250 billion for unpaid caregivers representing over 15 billion hours of service in 2020.[8] Direct cost of care for AD is estimated at $355 billion, with half of this amount absorbed by Medicare.[9]

The estimate of AD prevalence only includes those diagnosed after the onset of symptoms. However, there are many more individuals in the early stages of the disease, and if AD could be detected prior to symptoms developing, the number of individuals that could benefit from treatment would be significantly greater.

It is estimated that approximately 16% to 20% of individuals over 60 years old have MCI with the prevalence increasing as age advances.[10] About a third of those with MCI develop AD within 5 years,[11] a proportion that increases over periods greater than 5 years. While many studies have focused on later stages of the disease, it appears that a preventive approach may be more effective.

AD is usually associated with aging. The first signs of the disease are characterized by a loss in short term memory, followed by a progression to forgetfulness about one's own personal history and relationships. Behavioral changes, confusion about the date and time and becoming lost are other symptoms. In late-stage disease, AD patients cannot speak, total physical care is needed and the body begins to shut down. From the first concrete signs of the disease to death, the progression lasts an average of eight years, however, it can range from two to twenty years, depending on the person and other health conditions.

One of the difficulties with identifying AD is that there are few genetic indicators that allow us to anticipate those predisposed to the disease. The only way to definitively diagnose AD is with a tissue sample; however, brain imaging tests such as magnetic resonance imaging (MRI), computerized tomography (CT) and positron emission tomography (PET) are able to narrow down different types of degenerative brain disease. Biomarkers and risk factors can be evaluated to provide early indications of those who may be susceptible. About 1% of the AD population develops the disease as a result of certain genes that overexpress the amyloid precursor protein (APP), which results in early onset AD. Another group that suffers from AD at a high rate are the 400 thousand Americans with Down Syndrome. This group has an extra copy of chromosome 21, which also codes for the production of APP, leading to Aβ fragments that accumulate into toxic oligomers.

One gene that is closely associated with AD is the apolipoprotein E (APOE) gene on chromosome 19. There are a few forms of APOE, the ε2, ε3 and ε4 alleles. The ε3 allele is the most common and is thought to play a neutral role in the disease, while presence of the ε4 increases the risk of AD and several other diseases including atherosclerosis. Alleles come in pairs, and individuals with both alleles of ε4 are more susceptible to AD than those with one ε4 or no ε4 alleles.[12] It is thought that the ε2 and ε3 forms are more effective at breaking down Aβ than ε4, and the absence of these forms contribute to AD.

The most closely associated risk factor for AD is age. In a minority of cases, early onset Alzheimer's can occur in those under 65, but analysis of data indicates that about 5% of those with AD are in the 65 to 74 age range while 14% are in the 75 to 84 range. 72% of AD patients are 75 years old or greater.[13] Family history is also a predictor, but environmental factors and lifestyle also play a role.

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[8] Alzheimer's Association Factsheet. 2021 Alzheimer's Disease Facts and Figures.
[9] Alzheimer's Association Factsheet. 2021 Alzheimer's Disease Facts and Figures.
[10] Gillis, Cai, *et al.* The incidence of mild cognitive impairment: A systematic review and data synthesis. Alzheimer's Dement (Amst). 2019 Dec; 11: 248–256. Published online 2019 Mar 8. doi: 10.1016/j.dadm.2019.01.004
[11] Petersen RC, *et al*. Practice guideline update summary: Mild cognitive impairment. Neurology 2018;90(3):126-35.
[12] "Although 40-65% of AD patients have at least one copy of the ε4 allele, ApoE4 is not a determinant of the disease - at least a third of patients with AD are ApoE4 negative and some ApoE4 homozygotes never develop the disease. Yet those with two ε4 alleles have up to 20 times the risk of developing AD. There is also evidence that the ApoE2 allele may serve a protective role in AD. Thus, the genotype most at risk for Alzheimer's disease and at an earlier age is ApoE 4,4. Using genotype ApoE 3,3 as a benchmark (with the persons who have this genotype regarded as having a risk level of 1.0), individuals with genotype ApoE4,4 have an odds ratio of 14.9 of developing Alzheimer's disease. Individuals with the ApoE 3,4 genotype face an odds ratio of 3.2, and people with a copy of the 2 allele and the 4 allele (ApoE2,4), have an odds ratio of 2.6. Persons with one copy each of the 2 allele and the 3 allele (ApoE2,3) have an odds ratio of 0.6. Persons with two copies of the 2 allele (ApoE2,2) also have an odds ratio of 0.6." Wikipedia contributors. (2018, May 1). Apolipoprotein E. In *Wikipedia, The Free Encyclopedia*. Retrieved 14:06, May 6, 2018, from https://en.wikipedia.org/w/index.php?title=Apolipoprotein_E&oldid=839158512
[13] Alzheimer's Association Factsheet. 2021 Alzheimer's Disease Facts and Figures.

Formation of Plaques

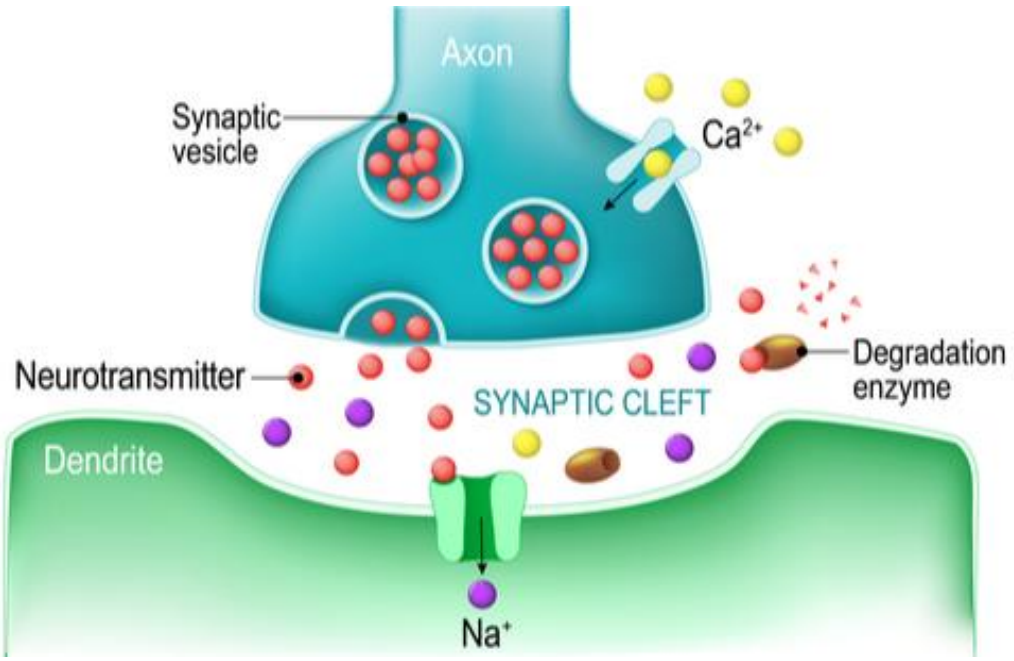
Autopsies consistently show the formation of Aβ plaques in the brains of those suffering from AD. The presence of Aβ is a natural occurrence and the body clears it through enzymatic and non-enzymatic pathways. However, in some cases, excessive Aβ is produced and insufficiently cleared, resulting in the buildup of toxic forms of the peptide which damage and destroy neurons. Aβ fragments result from the cleavage of amyloid precursor protein (APP), which is expressed on the surface of cells. Normally, APP is cleaved with the enzyme α-secretase which produces soluble APP and C83. These proteins are disintegrated via normal metabolic processes. In a minority of cases APP is cleaved with β-secretase, which produces soluble APP β, which creates the precondition for γ-secretase to cleave APP again, producing Aβ monomers. These monomers (single strands of Aβ) then combine into oligomers (multiple strands of Aβ) and fibrils (larger masses of Aβ plaque).

In the early days of drug development for AD, it was thought that plaques were responsible for causing the disease under the amyloid hypothesis. This theory, which was first proposed in 1991, attributed AD to the accumulation of Aβ in the brain which exists in many forms including monomers, oligomers and fibrils and the first drugs developed focused indiscriminately on this target. However, as research has progressed, there is mounting evidence that plaque is not the problem but rather soluble toxic oligomers.[14,15]

Neurotransmission

In a healthy brain, communication between the various parts of the organ rely on nervous impulses from one neuron to another. The first neurotransmitter discovered that contributed to this process was acetylcholine (ACh). When two neurons are communicating, ACh is released from vesicles in the presynaptic neuron following an electrical impulse. The ACh crosses the synaptic cleft and binds to receptors on the postsynaptic neuron triggering another electrical impulse in the postsynaptic neuron. When AD takes over, neurons are destroyed, reducing the number of pathways the brain can use to communicate. The disease also decreases ACh concentration and function. Remaining neurons suffer from this deficit, negatively affecting the brain's ability to operate.

Exhibit II – Signal Transmission at The Synapse[16]



ACh is involved in the creation and retrieval of memory. It is an ester of choline and acetic acid that functions as a transmitter substance of nerve impulses within the central and peripheral nervous systems. The substance is synthesized in nerve terminals from acetyl coenzyme A and choline, in a reaction catalyzed by choline acetyltransferase. The chemical is stored in vesicles at the ends of neurons and when stimulated, the motor neuron releases ACh.

[14] Zhao, Li; *et al*. The Toxicity of Amyloid β Oligomers. Int J Mol Sci. 2012; 13(6): 7303–7327.
[15] https://alzres.biomedcentral.com/articles/10.1186/alzrt226
[16] Source: Shutterstock

After ACh is released from vesicles in the presynaptic terminal and passes across the synaptic junction (cleft) as a chemical message it is either broken down by the enzyme acetylcholinesterase or returned to the presynaptic terminal through reuptake. Acetylcholinesterase (AChE) resides in the synaptic junction and will clear the ACh synaptic cleft. When, as a result of neurodegenerative disease, the volume of ACh is reduced, insufficient amounts of ACh are able to cross the synaptic cleft to bind to the receptors on the other side. Embracing this concept, drug development targeted the inhibition of acetylcholinesterase, reducing the amount of ACh that is broken down. Inhibiting AChE permits a higher concentration of the neurotransmitter to bind to the receptor thereby allowing a stronger nerve impulse to be delivered.

Diagnosis

Alzheimer's Disease is only diagnosed with certainty by brain autopsy, which requires a microscopic examination of brain tissue identifying the characteristic plaques and neurofibrillary tangles. However, there are a number of other methods used that provide evidence of the disease prior to death. PET scans, Aβ concentration in cerebrospinal fluid (CSF), as well as cognitive and functional tests are used to render a diagnosis. A patient's individual background, along with familial history and behavioral observations are also used to conclude a cause. Memory testing is employed to determine if the disease is at an early, middle or late stage. Some examples of neuropsychological tests are the mini-mental state examination (MMSE), clinical dementia rating sum of boxes (CDR-SB), the mini-cog test and tests for depression, as this is usually contemporary with AD.

Treatment

Acetylcholinesterase Inhibitors and a N-methyl-D-aspartate (NMDA) Receptor Antagonists
Treatment for AD does not provide a clinically supported cure or even stop the progression of the disease; however, there are medicines available that will treat its symptoms. There are five approved branded medications available to treat the symptoms of AD. Three of them are in the cholinesterase inhibitor class, one is a N-methyl-D-aspartate (NMDA) receptor antagonist and the last is a combination of the two classes. Cholinesterase inhibitors treat symptoms related to memory, language, judgment and thought processes and they work by increasing levels of acetylcholine, a chemical that facilitates neuronal communication. Galantamine also enables nicotinic receptors to become more sensitive, thereby enhancing the effect. The NMDA receptor antagonist named memantine helps a patient improve memory, attention, reason, language and ability to perform simple tasks. The drug works by regulating glutamate, a chemical involved in information processing, storage and retrieval. In 2014, a combination therapy branded Namzaric was approved, which combines AChEI donepezil and NMDA receptor antagonist memantine.

Aducanumab
The first new drug to be approved for AD in almost 20 years came to market last year. Aducanumab followed a tortuous path full of ups and downs prior to the FDA's June 2021 approval. The process and decision to allow the drug to be marketed was controversial as it was approved on surrogate endpoints that have not been directly tied to clinical benefit. Aducanumab's sponsor Biogen must conduct a post-marketing confirmatory study that will examine direct measures of efficacy. The trial is expected to take four years to complete. Despite a number of missteps by Biogen, post-approval safety concerns and CMS' limitation of Medicare coverage to aducanumab clinical studies, the approval of the drug has stimulated interest and investment in the AD space. FDA actions have shown that there is a regulatory pathway forward in AD and that the agency is committed to working with sponsors to advance new therapies in this space with few alternatives. Below we summarize the approved treatments for AD.

Exhibit III – AD FDA Approved Disease Modifying and Symptomatic Treatments[17]

Generic Name	Brand Name	Class	FDA Approved
donepezil	Aricept	Cholinesterase inhibitors	1996
galantamine	Razadyne	Cholinesterase inhibitors	2001
memantine	Namenda	NMDA (N-methyl-D-aspartate) receptor antagonist	2003
rivastigmine	Exelon	Cholinesterase inhibitors	2000
donepezil and memantine	Namzaric	Combination	2014
aducanumab	Aduhelm	Amyloid-β targeting monoclonal antibody	2021

Side effects such as nausea and vomiting for the oral AChEIs have prompted drugmakers to seek alternative methods of administration. Rivastigmine, for example, was reformulated as a patch and donepezil is being developed as a transdermal, helping reduce these unwanted side effects. Memantine has been evaluated as a patch and is also available in an extended-release formulation.

In Development

A May 2021 report by the Alzheimer's Association found that there are 126 agents in 152 trials investigating AD. 28 of them are in Phase III, 74 are in Phase II and 24 are in Phase I. By category, most (82.5%) target disease modification, while 10.3% are cognitive enhancement agents and 7.1% are being developed to reduce neuropsychiatric symptoms.[18] Of the disease modifying therapies, 15% target amyloid-β while 11% zero in on tau. Across all disease modifying therapies in all phases, ~30% are biologics and 70% are small molecule drugs. 40%, or a total of 50 are repurposed agents.

Of the disease modifying therapies, most of the Phase III candidates are small molecules including vTv Therapeutics' azeliragon, Anavex Life Sciences' blarcamesine, and TauRx Therapeutics' TRx0237 (LMTM) among others. The most visible programs feature monoclonal antibodies. Some of these leading Phase III candidates include Eli Lilly's (LLY) amyloid-β targeting donanemab, Roche's gantenerumab and Eisai/Biogen's lecanemab.

505(b)(2) Regulatory Pathway

There are multiple pathways available to obtain FDA drug approval. For new drug products that have not yet been evaluated by the FDA, a new drug application [NDA or 505(b)(1) route] is submitted. If the drug qualifies as a generic and is an exact chemical replica of a branded product, it may apply for approval using an abbreviated new drug application [ANDA-submitted under 505(j)]. If a sponsor and manufacturer want to make an improvement or modification to a previously approved drug, they may use the 505(b)(2) pathway.

The Drug Price Competition and Patent Term Restoration Act of 1984 added new routes for obtaining approval for drugs, including 505(j) and 505(b)(2). For 505(b)(2) in particular, this allows a method for companies that want to pursue a new dosage, new combination, new route of administration, prodrug enhancement or other modification. A bridge between the reference studies and the new product must be conducted which may include new clinical trials, other pharmacokinetic studies or bioavailability (BA) and bioequivalence (BE) studies.

While reference material related to safety and efficacy from the innovator may be used in a 505(b)(2) application, the chemistry, manufacturing and controls (CMC) section of the marketing application must be specific to the new product. The manufacturer must meet current Good Manufacturing Practice (cGMP) standards demonstrating the product's identity, strength, quality, potency, purity and stability.[19]

Designation as a new chemical entity (NCE) by the FDA is an important distinction for a prodrug seeking the 505(b)(2) pathway as it confers five years of market exclusivity if approved.

Using 505(b)(2) is an efficient mechanism that can save time and expenses for the sponsor allowing the use of reference drug studies to obtain approval. While some bridging studies are usually required, the development process is substantially shorter than that required for 505(b)(1) and the route also has a higher likelihood of approval compared with an NDA. Approval confers a period of market exclusivity as well that may exceed the molecule's patent protection. The common factor in 505(b)(2) submissions is that they all rely on existing material.

[17] Compiled by Zacks Analyst
[18] Cummings, J. *et al.* Alzheimer's disease drug development pipeline: 2021. 25 May 2021 https://doi.org/10.1002/trc2.12179
[19] Freije, I. *et al.* Review of Drugs Approved via the 505(b)(2) Pathway: Uncovering Drug Development Trends and Regulatory Requirements. Syneos Health, January 7, 2019

Candidates

ALPHA-1062

Alpha-1062 is a new chemical entity based on a pro-drug formulation of previously approved galantamine. Galantamine was FDA approved in February 2001 as a competitive and reversible inhibitor of acetylcholinesterase thought to enhance cholinergic function. It is approved for treatment of mild to moderate dementia of Alzheimer's patients.

Galantamine
Galantamine was first approved in Sweden in 2000 and later by the FDA in 2001 to treat Alzheimer's Disease. The drug was discovered in the 1950s and was derived from an alkaloid isolated from *Galanthus nivalis*, the common snowdrop. For those with an interest in Greek mythology, the plant is the antidote source used by the protagonist in Homer's Odyssey to protect him from Circe's potions. As the candidate moved from the world of myth to the laboratory and eventually into the clinic, galantamine was the subject of four randomized, double-blind, placebo-controlled trials enrolling 2,653 patients diagnosed with AD that supported its approval.

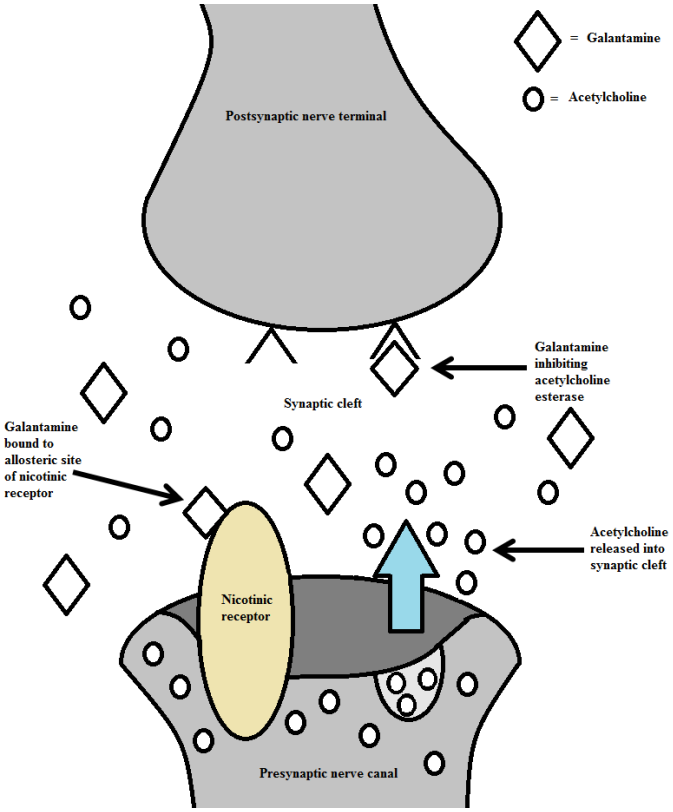
Exhibit IV – *Galanthus Nivalis*, The Common Snowdrop[20]

Results of the four studies evaluating the immediate-release tablet were measured using a dual outcome assessment strategy measured by the Alzheimer's Disease Assessment Scale (ADAS-cog) and the Clinician's Interview Based Impression of Change that required the use of caregiver information (CIBIC-plus). Results showed a statistically significant benefit from galantamine compared to placebo using both the ADAS-cog and CIBIC-plus scales.[21]

Mechanism of Action
Galantamine is a cholinesterase inhibitor that functions both as a reversible inhibitor of acetylcholinesterase and as an amplifier of acetylcholine on nicotinic receptors. Application of the drug leads to increased cholinergic neurotransmission in the brain. It blocks the breakdown of acetylcholine in the synaptic cleft, thereby preserving it for purposes of neurotransmission. Since the agent only maintains the levels of acetylcholine and does not slow the loss of acetylcholine-producing neurons, it is not considered a disease-modifying drug for AD.

[20] Source: Shutterstock
[21] Source: FDA Label for Razadyne

Exhibit V – Galantamine's MoA between Synapses[22]



Efficacy

A number of studies have measured galantamine's long term efficacy and have reported modest and consistent cognitive and clinical benefits over a multi-year period.[23] More than 90 clinical trials have investigated galantamine and its efficacy for AD. Wilcock *et al.*[24] observed a ~3 point treatment effect vs. placebo using both the ADAS-cognition scale and the CIBIC-plus and DAD scales of clinical impression. Behavioral symptoms including agitation, anxiety, disinhibition and aberrant movements were improved for galantamine patients as measured by the Neuro-psychiatric Inventory (NPI) and investigated in several trials.[25,26] Long-term efficacy studies demonstrated modest and consistent cognitive and clinical benefits over a multi-year period[27] and a later study has shown that treatment with galantamine can delay time to nursing home placement.[28]

Side Effects

While galantamine has demonstrated efficacy in cognitive and clinical aspects, patients have suffered serious skin reactions, bradycardia and heart block, gastrointestinal conditions related to excess gastric acid secretion. The most common adverse reactions that occurred at a rate 5% or greater include nausea, vomiting, diarrhea, dizziness, headache, decreased appetite and weight loss. Examining the FDA label for galantamine finds discontinuations due to adverse reactions in placebo controlled studies of almost 13% of patients. Specifically, the discontinuations were due to nausea (7.7%), vomiting (4.1%), diarrhea (0.9%), decreased weight (0.8%) and abdominal pain (0.5%) among others. Most of the negative side effects and discontinuations due to side effects were related to gastrointestinal (GI) issues and could potentially be solved by blocking the activity of the drug in the GI tract. With existing formulations of galantamine, a dose escalation period over several weeks is used to accustom the patient to the drug and reduce the impact of side effects.

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[22] By Strezza - Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=58335358

[23] Raskind MA, Peskind ER, Truyen L, Kershaw P, Damaraju CV. The cognitive benefits of galantamine are sustained for at least 36 months: a long-term extension trial. Arch Neurol. 2004 Feb;61(2):252-6. PubMed.

[24] Wilcock, G.K. *et al.* Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. BMJ, December 9, 2000.

[25] Herrmann N, Rabheru K, Wang J, Binder C. Galantamine treatment of problematic behavior in Alzheimer disease: post-hoc analysis of pooled data from three large trials. Am J Geriatr Psychiatry. 2005 Jun;13(6):527-34.

[26] Kavanagh S, Gaudig M, Van Baelen B, Adami M, Delgado A, Guzman C, Jedenius E, Schäuble B. Galantamine and behavior in Alzheimer disease: analysis of four trials. Acta Neurol Scand. 2011 Nov;124(5):302-8.

[27] Raskind MA, Peskind ER, Truyen L, Kershaw P, Damaraju CV. The cognitive benefits of galantamine are sustained for at least 36 months: a long-term extension trial. Arch Neurol. 2004 Feb;61(2):252-6.

[28] Feldman, Howard, *et al.* Treatment with galantamine and time to nursing home placement in Alzheimer's disease patients with and without cerebrovascular disease. Int Journal of Geriatric Psychiatry 2009;

Galantamine Pivotal Trials in AD[29]
Multiple Phase III trials were launched by Johnson & Johnson Pharmaceutical Research in the late 1990s to measure the effect of galantamine on patients with AD. The studies were randomized, double-blind, placebo-controlled trials conducted around the globe. Various doses were used to identify optimal efficacy and tolerability.

Cognition was measured using the cognitive subscale of the ADAS-cog, activities of daily living (ADL) and behavioral symptoms. All trials demonstrated benefits for cognitive function versus placebo. Patients that received a 24 mg/day dose performed better than patients who initially started on placebo then later switched to the drug arm, suggesting that early treatment can stem the decline in patients in a benefit that cannot be compensated for by dosing later.

A six-month US study that was followed by a six-month extension found that patients on drug for the full 12 months maintained functional abilities while patients on placebo for the first six months experienced significant decline.[30] The use of galantamine also showed evidence of delaying the start of behavioral symptoms[31] as measured by the neuropsychiatric inventory (NPI) score. Of the components used in the NPI score, patients evidenced the most benefit in symptoms of aberrant motor behavior, anxiety, disinhibition and hallucinations. Caregivers in this study participating in the placebo group suffered increasing distress whereas those in the galantamine groups maintained NPI scores close to baseline.[32]

Other studies measuring the effects of galantamine demonstrated benefits on patients' sleep quality and on caregiver burden. In contrast to rivastigmine and donepezil, the FDA label for galantamine does not list insomnia as a side effect, giving the product a significant advantage compared to its competitors in an elderly patient population that is frequently plagued by sleep problems. A study by Naharci *et al.* found that sleep quality was better in patients treated with galantamine compared to other study arms with rivastigmine and donepezil.[33]

Long-Term Use of Galantamine[34]
A study examining AD patients in the Swedish Dementia Registry (SDR) conducted by several researchers in Sweden (Xu *et al.)* sought to determine whether acetylcholinesterase inhibitors (AChEIs) were associated with slower cognitive decline and decreased risk of severe dementia or death. The study included almost 17,500 patients that were evaluated over a five-year period to determine the impact of AChEIs. Of the 11,652 patients using AChEIs, administration of donepezil was 62%, galantamine 21% and rivastigmine 17%.

The article references various other AChEI investigations concluding that the drug class provided benefits in cognition and cost efficiency in a variety of settings. Other studies have revealed an association between the use of AChEIs and decreased risk of myocardial infarction, stroke and death in patients with dementia. The article noted the lack of long-term research examining the effectiveness of AChEIs in AD after one year of treatment which provided the impetus for the Xu piece.[35] Xu *et al.* examined AD data over a five-year period for patients in the SDR database. While high attrition and loss to follow up make these studies difficult, access to the SDR provided a unique resource where patients are more consistently diagnosed and followed annually, generating cognitive evaluation and other critical data.

Results from the analysis provided conclusions supportive of long-term use of AChEIs and galantamine in particular. When results of the data were stratified by separate AChEIs, only galantamine users had a statistically significant lower risk of severe dementia. Patients who did not take AChEIs were older, had lower MMSE score and presented a greater number of comorbid conditions such as cardiovascular disorders. They also took more medications than treated patients. AChEI users had a 27% lower risk of death. When comparing the three measured

[29] Information in this section is summarized from Lilienfeld, S. Galantamine — a Novel Cholinergic Drug with a Unique Dual Mode of Action for the Treatment of Patients with Alzheimer's Disease. Janssen Research Foundation, Titusville, New Jersey, 08560, USA
[30] Wilcock, G.K. *et al.* Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. Galantamine International-1 Study Group. BMJ. 2000 Dec 9;321(7274):1445-9. doi: 10.1136/bmj.321.7274.1445.
[31] The most common AD behavioral symptoms include getting upset, worried and angry more easily, depression, aggression, anger, anxiety, agitation and general emotional distress. The individual may have physical or verbal outbursts, have hallucinations and show signs of restlessness among others.
[32] Tariot, P.N. *et al.* A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. Neurology. 2000 Jun 27;54(12):2269-76. doi: 10.1212/wnl.54.12.2269.
[33] Naharci M.I. *et al.* Galantamine improves sleep quality in patients with dementia. Acta Neurol Belg. 2015 Dec;115(4):563-8. doi: 10.1007/s13760-015-0453-9. Epub 2015 Mar 17.
[34] Information from this section is summarized from Hong Xu, MD, PhD, Sara Garcia-Ptacek, MD, PhD, Linus Jonsson, PhD, Anders Wimo, MD, PhD, Peter Nordstrom, MD, PhD, and Maria Eriksdotter, MD, PhD. Long-term Effects of Cholinesterase Inhibitors on Cognitive Decline and Mortality. Neurology 2021;96:e2220-e2230. doi:10.1212/WNL.0000000000011832
[35] Hong Xu, MD, PhD, Sara Garcia-Ptacek, MD, PhD, Linus Jonsson, PhD, Anders Wimo, MD, PhD, Peter Nordstrom, MD, PhD, and Maria Eriksdotter, MD, PhD. Long-term Effects of Cholinesterase Inhibitors on Cognitive Decline and Mortality. Neurology 2021;96:e2220-e2230. doi:10.1212/WNL.0000000000011832

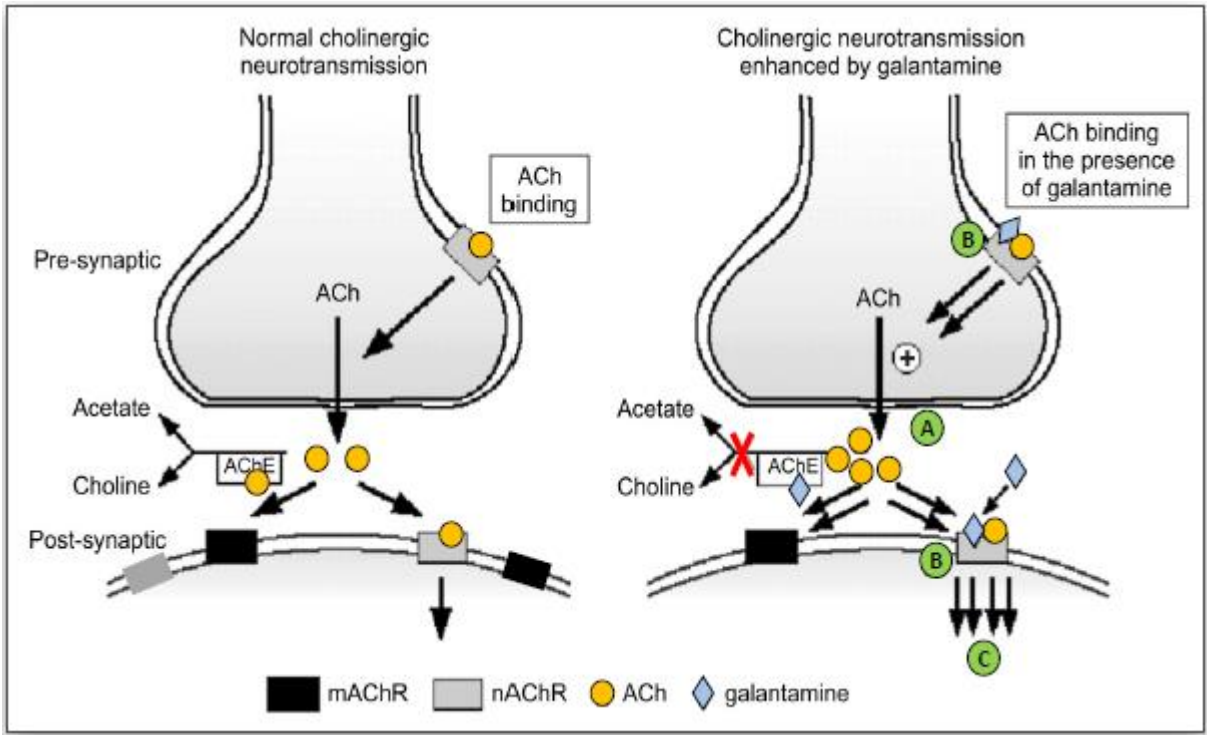
AChEIs, donepezil, rivastigmine and galantamine, only the last mentioned was associated with a reduction in cognitive decline over time. While the effect was modest, it persisted over the five years of data measurement. Galantamine use was associated with reduced risk for severe dementia and mortality and had the largest effect size for the association with cognitive decline in the study. AChEIs are associated with cognitive benefits that are modest but persist over the long term.

A Prodrug of Galantamine

Prodrugs are inactive precursors to a pharmacologically active drug that are converted to active form after undergoing a chemical or enzymatic process in the body. A variety of approaches can be used to formulate the prodrug including adding chemical groups to the core molecule which are then cleaved, activating the compound. Esters are an especially appealing modification as this functional group can improve lipophilicity for passive membrane transport or increase the aqueous solubility of the active drug. Prodrugs are in many cases able to solve poor biopharmaceutical performance related to absorption, distribution, metabolism, excretion and toxicity. The structural modification into a prodrug can improve solubility, stability, activity, ability to reach the site of action, release characteristics and reduce toxicity. Near 10% of new drugs approved are prodrugs, demonstrating the broad acceptance of this approach.

Primary benefits of using a prodrug are increased solubility and lipophilicity, selective targeting, protection from rapid elimination and improved compliance due to fewer negative side effects. As the drug remains inactive until it is metabolized, there is increased bioavailability and less variability in delivery to the target site.

Exhibit VI – Galantamine Enhances ACh Levels and Nicotinic Receptor Sensitivity[36]



A prodrug formulation can improve the bioavailability of a molecule, as many are broken down in the gastrointestinal tract. The addition of a polar molecule such as certain esters and amide groups can help drug absorption and allow it to reach the target tissue in a high enough concentration to be effective. Site specific targeting is another important feature of prodrugs. As AChEIs cause unwanted side effects in the gut and perform their function in the brain, avoiding the former and targeting the latter provide a strong justification for a prodrug that enables this refinement. Galantamine, in particular, as an AChE inhibitor overstimulates the neurons in the gut lumen and causes nausea, vomiting and diarrhea. In contrast, Alpha-1062 is absorbed as an inert drug in the intestine, avoiding interaction, and is later converted into the active form of the drug in the liver. The drug then passes into the bloodstream, meets and crosses the blood brain barrier and finally travels to the inter-synaptic space where it inhibits AChE and acts as an allosteric potentiator of nicotinic acetylcholine receptors (nAChRs).

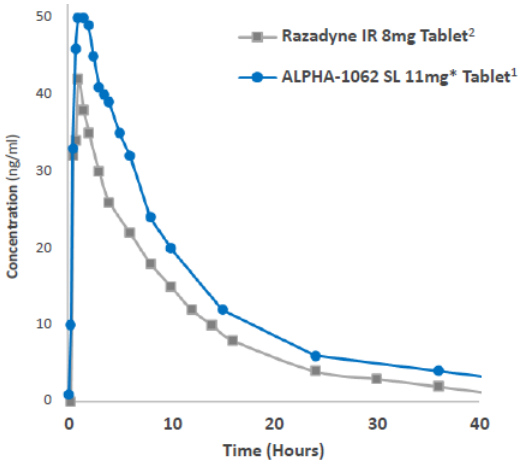
[36] Source: Alpha Cognition January 2022 Corporate Presentation

Alpha-1062 adds a benzoyl ester and gluconate salt to galantamine to eliminate AChE inhibition and increase solubility respectively. The modification of galantamine into a prodrug alters the product sufficiently to be considered a new chemical entity (NCE).

The leader in the AChEI space is Aricept (donepezil), which commands over half of the market. One of the key side effects that plagues donepezil patients is insomnia with 14% initially experiencing the effect at 10mg/day.[37] If galantamine's prodrug formulation is able to sidestep the GI-related side effects, it becomes a formidable competitor to donepezil as insomnia is not listed as a side effect for galantamine.

Bioequivalence
To receive approval via the 505(b)(2) pathway, Alpha-1062 must show bioequivalence to galantamine. In preclinical work, the bioequivalence study showed a similar profile with 15% greater area under the curve (AUC), 14% greater C_{MAX}, and 1.4 hour later T_{MAX}.

Exhibit VII – Alpha-1062 Bioequivalence/Bioavailability vs. Galantamine (Razadyne)[38]



Pharmacokinetic Parameter	ALPHA-1062 11 mg Sublingual (n=10)	ALPHA-1062 11 mg Enteric Coated (n=10)	RAZADYNE 8 mg IR (n=10)
AUC	523	519	451
Cmax (ng/mL)	52.7	52.9	46.3
Tmax (h)	1.5	2.5	1.1

90% Confidence Interval (CI) acceptance criteria is 80-125% for the test/reference ratio

Additional studies required include a food effect study and fasted study that will use a single dose, crossover design under both fed and fasted conditions. 32 healthy adult subjects will be evaluated in each study with a requirement that there be a 90% confidence interval for pharmacokinetic parameters for AUC and a C_{MAX} from 80% to 125% of the approved product.

While there is great hope that a clinically proven disease modifying therapy will come to the rescue, given the uncertain results for aducanumab, a better alternative may be to postpone long term decline in patients. In a progressive condition such as AD, extending the period of health significantly may be the best option and a favorable alternative over transient short-term improvements. Cholinesterase inhibitors have demonstrated in multiple studies that they provide benefits for cognitive and functional abilities, behavioral symptoms and caregiver burden as compared to placebo. The drug's dual mechanism of action acts by both inhibiting AChE, thereby increasing the volume of ACh in the inter-synaptic space and by modulating nAChRs to enhance the cellular response induced by ACh. Allosteric modulators, such as galantamine, cannot activate nAChRs on their own and require that galantamine and ACh bind simultaneously to their respective binding sites on the same nAChR to benefit from the enhanced effect induced by ACh.

Research has established that galantamine allosterically modulates nAChRs by binding to a secondary binding region on the α-subunit distinct from the ACh site.[39,40] When galantamine and ACh simultaneously bind to the nAChRs, the response triggered by ACh is enhanced. According to Lilienfeld,[41] this feature was not observed in other approved or previously investigated products in the class including rivastigmine, donepezil, tacrine or metrifonate.

[37] Source: FDA Label for Aricept
[38] Source: Alpha Cognition Corporate Presentation January 2022.
[39] Maelicke A, Samochocki M, Jostock R, *et al*. Allosteric sensitization of nicotinic receptors by galantamine, a new treatment strategy for Alzheimer's disease. Biol Psychiatry 2001;49:279–288.
[40] Samochocki M, Zerlin M, Jostock R, *et al*. Galantamine is an allosterically potentiating ligand of the human α4/β2 nAChR. Acta Neurologica Scandinavica 2000;102 (Suppl 176):68–73.
[41] Lilienfeld, S. Galantamine - a Novel Cholinergic Drug with a Unique Dual Mode of Action for the Treatment of Patients with Alzheimer's Disease. CNS Drug Reviews Vol. 8, No.2, pp. 159–176 © 2002 Neva Press, Branford, Connecticut

Alpha-1062 Mild Traumatic Brain Injury (mTBI) Program

Alpha-1062 is being investigated in mild traumatic brain injury and is at a preclinical stage of development. According to the Management of Concussion and Mild Traumatic Brain Injury 2020 data, three million individuals are affected by this condition in the United States annually. In contrast to the oral form administered for AD, Alpha-1062 for mTBI will be administered using a nasal spray. A mammal model is being investigated to determine neurobehavioral and cognitive improvement of drug treatment, as compared to injured without treatment and uninjured cohorts in a three-arm study. In December, results of the neurobehavioral and cognitive improvement were released and demonstrated a statistically significant improvement in treated animals over their untreated counterparts. Furthermore, results for treated injured animals obtained results equal with uninjured animals in four of five neurobehavioral primary endpoints. Additional histology work was discussed in a press release and analyst call and will be presented at an upcoming conference. Results showed a dramatic benefit from Alpha-1062 where sufficient brain was saved in treated animals compared with vehicle. All IND studies have been completed and next steps are to meet with the FDA which is expected to occur in the latter part of 2Q:22. If the IND is cleared by the FDA, the mTBI program could advance immediately to a Phase II study.

Summarized findings from the histological pre-clinical study of Alpha-1062 vs. vehicle in mTBI:

- Demonstrated statistically significant reduction in lesion size measured at 35 days after injury;
- Preserved greater hippocampal structure - the hippocampus plays a critical role in learning, memory formation, and spatial coding and damage to hippocampus can lead to memory disorders like AD, amnesia, and depression;
- Demonstrated statistically, significant reduction in neuronal cell loss. The number of neurons in the Alpha-1062 treated animals were equivalent to those in the uninjured cohort of animals at the end of treatment;
- Observed statistically significant enhanced neurogenesis as evidenced by an increase in the number of neuron precursor cells and new neurons in the dentate gyrus, which plays a critical role in learning, information processing and mood regulation.

Alpha-0602 (Progranulin) For Amyotrophic Lateral Sclerosis

Alpha-0602 is being developed as a gene therapy for the treatment of Amyotrophic Lateral Sclerosis (ALS) and has been granted Orphan status by the FDA. Progranulin was discovered in 2006 and is a secreted growth factor that is associated with a number of biological processes including inflammation, wound healing and cancer. Progranulin protects the brain through its function as an autocrine neurotrophic factor and increases the activity of cell survival signaling pathways. Alpha Cognition's program would deliver gene constructs to neurons using an adeno associated virus (AAV) system.

Alpha Cognition has researched progranulin in an animal model with the ALS neurological disorder. Results of animal study work indicate that increasing progranulin levels may be effective in modifying the disease process. Milestones for preclinical efforts and selection of a primary biological drug candidate are expected to be completed in 2Q:22. An IND is expected to be filed in 2023 after additional safety studies have been completed.

Alpha-1062 plus Memantine

There is one approved, branded combination drug approved for symptomatic use in AD. This product, registered as Namzaric, married the generic donepezil and memantine to simplify administration of the drug for moderate to severe AD patients. It was approved in 2014 and has been able to generate from $200 to $300 million in revenues each year from 2017 to 2020. Alpha Cognition estimates that it can improve on the performance of Namzaric by combining its prodrug formulation (Alpha-1062) of galantamine with memantine. In contrast to donepezil, Alpha-1062 has a dual mechanism of action that decreases acetylcholinesterase in the synaptic cleft and enhances the sensitivity of nicotinic acetylcholine receptors. Alpha-1062 is also expected to have an improved side effect profile compared with donepezil, with no insomnia and improved GI-related side effects due to its prodrug formulation. Formulation efforts are underway and the product, if granted IND clearance, would conduct trials and pursue the 505(b)(2) regulatory pathway with the FDA.

Alpha Cognition Pipeline

In addition to the lead program in primary pursuits in AD for with Alpha-1062, Alpha Cognition is advancing its lead compound in mild traumatic brain injury (mTBI) and Alpha-0602 in a gene therapy for amyotrophic lateral sclerosis. Below we include the company's pipeline which provides a summary and status of the clinical and early-stage programs underway.

Exhibit VIIII – Alpha Cognition Pipeline[42]

Indication	Preclinical	Phase 1	Phase 2	Phase 3 / Pivotal	Status / Upcoming Milestones
Alzheimer's Dementia					
ALPHA-1062 Enteric-coated Tablet					Pivotal Study Top-line Results Q2/22 Pt Tolerability Study Starts Q2/22 NDA filing Q3/22
ALPHA-1062 + Memantine					Formulation development ongoing for 505(b)(2) regulatory pathway
Mild Traumatic Brain Injury					
ALPHA-1062 Intranasal Formulation					Preclinical Top-line Results Q1/22 Phase 1 studies completed IND Submission Q4/22
Amyotrophic Lateral Sclerosis					
ALPHA-0602 Progranulin					Progranulin Gene therapy approach for ALS – 2nd animal study initiated Q4/21 Preclinical Study Top-line Results Q1/22

[42] Alpha Cognition Corporate Presentation, January 2022

Intellectual Property and Patents

Alpha Cognition has been granted a number of patents based on therapeutic use for Alpha-1062 that cover multiple neurological diseases characterized by cholinergic deficit. Further protection for the compound is supported by use of the prodrug formulation. Delivery, polymorph and formulation patents have also been granted. There is potential that effective patent protection of Alpha-1062 and therapeutically relevant salts, polymorphs and/or related formulations can be extended beyond 2042.

Key Patents Alpha-1062:

- Derivatives of galantamine as pro-drugs for the treatment of human brain diseases
  - Granted in Canada, China, Japan, Europe & US; PCT application;
  - Protects the therapeutic use of Alpha-1062 to treat a variety of neurodegenerative, psychiatric or neurological diseases with a cholinergic deficit;
  - Two US patents are allowed in this family that cover the corresponding method of treatment claims, both without limitation to administration forms, one of which is directed to the nasal route;
  - Expiry April 2028;
  - Seeking patent term extension in the US (9,763,953).
- Enhanced brain bioavailability of galantamine by selected formulations and transmucosal administration of lipophilic prodrugs
  - Granted in Australia, Europe, Japan & Canada;
  - Protects therapeutic use of Alpha-1062 and corresponding pharmaceutical compositions in the treatment of brain disease associated with cognitive impairment, wherein the claims cover intranasal, sublingual or buccal administration of the gluconate, saccharate or lactate salt of Alpha-1062;
  - Pending in China and the US.

Patents Pending Alpha-1062:

- Self-preserving compositions and multi-use dispensers for administering Alpha-1062
  - Based on the discovery that Alpha-1062 exhibits potent anti-microbial properties which enables self-preserving formulations to be used without additional preservatives.
- Solid Forms of Alpha-1062 Gluconate
  - Based on the discovery and isolation of multiple unique crystalline forms of the Alpha-1062 gluconate salt where a stable, highly soluble polymorph form was identified, demonstrating improved stability and solubility over other crystalline forms and is intended for use in the drug product.
  - Expiry in 2041 (Europe) and 2042 (US & PCT)
- Alpha-1062 for Treating Mild-Traumatic Brain Injury (mTBI)
  - Based on preclinical animal model studies in mTBI showing enhanced therapeutic benefit, suited for multi-use intranasal administration, building on the antimicrobial properties of the active pharmaceutical ingredient;
  - Potential for patent protection until 2042.

Key Patents Alpha-0602

- Treating neurodegenerative diseases with progranulin
  - Granted in China, India, Europe and pending in US and Canada;
  - Protects the therapeutic use of Alpha-0602 to treat a variety of neurodegenerative or neurological diseases;
  - The parent European patent was restricted to Parkinson's and Alzheimer's Disease;
  - A divisional patent was filed and granted in Europe covering the treatment of any neurodegenerative disease using progranulin via gene or protein therapy.
- Method for increasing neprilysin expression and activity
  - Filed 2011, expiry 2031.
- Granulins or Combinations thereof to Treat Neurodegenerative Disease
  - Filed 2021, expiry 2042.

Financial and Operational Results

Recent Achievements

- Single ascending dose (SAD) study for Alpha-1062 in AD – 2021
- Multiple ascending dose (MAD) study for Alpha-1062 in AD – 2021
- Alpha-1062 pivotal trial launch in AD – 3Q:21
- Alpha-1062 completion of pivotal trial work in AD – 2Q:22
- Alpha-1062 pivotal trial topline announcement in AD – 2Q:22
- Alpha-1062 NDA submission in AD – 3Q:22
- Alpha-1062 potential FDA approval in AD – 3Q:23

2021 Financial and Operational Results

In March 2021, Alpha Cognition completed a reverse merger that allowed it to become public and trade on Toronto's TSX Venture Exchange. Michael McFadden was named chief executive officer (CEO) the following month. Other team members were also added in the following weeks including Lauren D'Angelo as chief commercial officer (CCO). By the end of summer 2021, the company had been approved for an additional listing on the OTCQB Venture Market and chief financial officer (CFO) Jeremy Wright had been added to the executive team. In December, chief medical officer (CMO) Cedric O'Gorman was appointed to assist in the clinical development of the company's pipeline.

Operational achievements include the FDA acceptance of the Investigational New Drug (IND) application for Alpha-1062 for mild to moderate AD and sharing of preclinical data for Alpha-1062 in mild traumatic brain injury.

In the fall, Alpha Cognition was able to successfully raise CAD$14.4 million in gross proceeds, selling 9.6 million shares at CAD$1.50 and issuing 9.6 million warrants with an exercise price of CAD$1.75. 660,000 broker warrants were also issued, each entitling the holder to purchase a share at CAD$1.50.

Alpha Cognition reported third quarter 2021 results with a SEDAR filing on November 26, 2021 and issuance of a press release on November 30th. No revenues were reported and operating expense totaled ($2.1) million producing a net loss of ($4.3) million or ($0.09) per share.

For the third quarter of 2021 versus the third quarter of 2020, both ending September 30th:

- Research and development expenses totaled $2.1 million, up 99% from $1.1 million on higher product development costs and compensation;
- General and administrative expenses rose 68% to $340,000 from $202,000 on higher compensation and expenses allocated toward investor relations activities;
- Total operating expenses rose 103% to $3.1 million from $1.5 million;
- Net other items were ($1.2) million dominated by loss on revaluation of derivative liability;
- Net loss was ($4.3) million vs. ($1.4) million or ($0.09) and ($0.03) per share, respectively.

As of September 30, 2021, cash and equivalents totaled $4.7 million. This amount compares to a $5.9 million at the end of December 2020. In terms of debt, Alpha Cognition carries a promissory note issued in March 2015 to Neurodyn Life Sciences for the acquisition of Alpha-1062 held on the balance sheet at $1.0 million. Cash used in operations for the first nine months of the year was ($6.2) million compared with cash used of ($3.7) million in the prior year nine month period. Financing cash flows totaled $4.6 million, bolstered by funds generated by share issuances and warrant exercises, partially offset by share issuance costs.

Following the end of quarter, on October 1st, 2021 the company closed a CAD$14.4 million public offering, which was equivalent to approximately $11.4 million in US dollars using exchange rates at the time. We estimate net funds of about US$10.6 million were added to the company's coffers as a result of the raise.

Alpha Cognition Upcoming Milestones

- Alpha-1062 pre-clinical top-line results in mild TBI – 1Q:22
- Alpha-0602 (gene therapy) pre-clinical results – 2Q:22
- Alpha-1062 pivotal trial results in AD – 2Q:22
- Alpha-1062 patient tolerability study start in AD – 2Q:22
- NDA submission for Alpha-1062 in AD – 3Q:22
- IND submission for Alpha-1062 in mild TBI – 4Q:22
- Alpha-0602 pre-clinical study (2nd mammal) start – 4Q:22
- Alpha-1062 potential FDA approval for mild to moderate AD – 2Q:23
- Alpha-1062 patient tolerability study topline results in AD – 2Q:23
- Alpha-0602 2nd mammal pre-clinical study top-line results – 2Q:23
- Alpha-1062 potential label change – 4Q:23
- Initiation of Alpha-1062 combination (BABE) study – 4Q:23

MANAGEMENT & LEADERSHIP

Michael McFadden – Chief Executive Officer

Mr. McFadden brings more than 30 years of successful leadership experience spanning pre-IND drug discovery to commercialization and has launched over a dozen therapies in neurology, psychiatry, endocrinology and urology. Mr. McFadden most recently served as chief commercial officer of Mpower Health, an orthopedic healthcare services company focused on value-based care solutions and interoperative neuromonitoring clinical services. Previously, Mr. McFadden had served on executive teams with Urovant Sciences, a urology based public company, and Avanir Pharmaceuticals, a CNS focused company, which was purchased by Otsuka Pharmaceutical Co, Ltd. in 2015. Earlier in his career, Mr. McFadden served in leadership roles at Amylin Pharmaceuticals, Pharmacia, and Eli Lilly and Company. He serves on advisory boards for Mpower Health, and also MindLab, LLC, a company focused on therapeutics for pain management. Mr. McFadden holds a Bachelors in Business Administration from Northeast Louisiana University.

Cedric O'Gorman, MD – Chief Medical Officer

Dr. O'Gorman brings to Alpha Cognition more than two decades of life sciences experience in clinical development, medical affairs and medical strategy, almost exclusively in the CNS therapeutic space, and across all stages of drug development. Prior to joining Alpha Cognition, he served as Senior Vice President, Clinical Development and Medical Affairs at Axsome Therapeutics where he led clinical development programs for therapeutic indications which included major depressive disorder, agitation associated with Alzheimer's disease, narcolepsy, and migraine. Prior to Axsome, Dr. O'Gorman was Vice President of Medical Affairs at Intra-Cellular Therapies and before that, Dr. O'Gorman was the U.S. Medical Lead for Psychiatry at Genentech/Roche. Prior to this, he spent 5 years at Pfizer representing medical affairs on several branded neuroscience products for schizophrenia, bipolar disorder, and major depressive disorder.

Lauren D'Angelo – Chief Commercial Officer

Ms. D'Angelo brings more than 20 years' experience leading successful drug commercialization efforts across 10 therapeutic areas, including multiple CNS therapies. She most recently served as Vice President, Marketing and Commercial Strategy at Urovant Sciences, where she led the commercial launch of GEMTESA, the first new Overactive Bladder (OAB) drug treatment in more than 10 years. Prior to Urovant Sciences, Ms. D'Angelo held leadership roles in commercial development, marketing, operations and sales at Avanir Pharmaceuticals, Medivation, Genentech, and AstraZeneca. She has participated in more than 10 successful pharmaceutical drug launches, six of which have become blockbuster brands. Ms. D'Angelo was recognized as Medical Marketing & Media's 2017 Woman to Watch and was selected as one of Pharmaceutical Executive's Emerging Pharma Leaders for 2020. Ms. D'Angelo received her B.S. in Management Information Systems and Finance from Florida State University and her MBA from the University of Florida.

Denis Kay, PhD – Chief Scientific Officer

Dr. Kay founded the entity that conducted early clinical trials for ALPHA-1062, Neurodyn Life Sciences (NLS), in August 2006 and has acted as NLS's Chief Scientific Officer for the last 14 years and Alpha Cognition's Chief Scientific Officer since 2017. Dr. Kay has more than 25 years of experience in the development and characterization of neurological conditions. He is a grant recipient of the Michael J. Fox Foundation and has received funding from numerous agencies for research and product development programs. Dr. Kay is a graduate of Dalhousie (B.Sc. and M.Sc.) and McGill (Ph.D.) Universities and has contributed publications to over 40 scientific journals. Dr. Kay also held teaching assistantship positions at Dalhousie and McGill Universities, and was a lecturer at McGill University.

Jeremy Wright – Chief Financial Officer

Mr. Wright has broad experience working with senior management developing strategies and solutions to business issues mainly related to corporate finance, cost and risk management, and governance. Mr. Wright is a Chartered Professional Accountant (Certified Management Accountant), currently serves as President and CEO of Seatrend Strategy Group and as a director for several public and private companies including: Pontus Protein Ltd., Centurion Minerals Ltd., and Demetra Minerals Inc. Mr. Wright previously served as a director of TGS Esports Inc., Freeform Capital Partners Inc., Pacific Community Resources Society and the Canadian Freestyle Ski Association. In addition, Mr. Wright also serves as the CFO for several public and private companies, including: the Target Company, Portofino Resources Inc., and Centurion Minerals Ltd. He was previously the CFO for GTEC Cannabis Co., an ultra-premium cannabis producer having three federally licensed production facilities across Canada. Mr. Wright also holds a Bachelor of Arts, with honors in Environmental Economics, from Brock University.

RISKS

All investments contain an element of risk which reflects the uncertainty of a business and what it will ultimately achieve. Some investments exhibit higher predictability, with current cash flows and established sales. These enterprises will have a lower level of perceived risk while other companies that are developing an undefined, new technology have a much higher level of perceived risk.

The biotechnology space includes companies at both ends of the spectrum, from mega-cap pharmaceutical powerhouses that have multiple products currently generating revenues, to small operations with a handful of employees conducting pre-clinical studies. Many of the risks faced by the large pharmaceutical companies and smaller biotechnology-focused firms are similar; however, there are some hazards that are particular to smaller companies that have not yet established themselves or their products.

For smaller early-stage companies, investing in drug development is a lengthy process. The timeframe for conducting pre-clinical research to eventually commercializing a drug can take from 12 to 15 years or even longer given market and company-specific conditions. And with, on average, only one in one thousand compounds eventually making it to the market from the preclinical stage, the risks are substantial. Expedited pathways to approval are available which include the 505(b)(2) pathway for new formulations of previously approved active ingredients which can dramatically shorten the timeframe. Alpha Cognition's lead candidate is advancing using the 505(b)(2) route, which will rely on studies performed on behalf of the reference product.

Even if a company has a strong, experienced team that is developing a therapy with a high likelihood of success and a large addressable market, securing funding may be difficult. Access to financing comes and goes in cycles. During periods of improving confidence, capital may be easy to obtain; however, during a liquidity crisis or a period of heightened risk perception, even companies with bright prospects may be in trouble if they are dependent on the financial markets to fund their work. If capital is needed to sustain operations and it is not readily available, the company may be forced to suspend research and development, sell equity at a substantial discount to previous valuations and dilute earlier shareholders. A lack of funding may leave potentially promising therapies without a viable route to move forward or force a company to accept onerous terms.

All drugs must navigate the regulatory approval process in the US, EU, Latin America, Japan and other countries before commercialization. Success is uncertain and may take years depending upon the needs and desires of the determining authority. Substantial expense is undertaken to bring a molecule or compound through clinical trials and address all of the regulatory agencies' concerns. Isolating companies that have a long history of research success in drug development, with opinion leaders and experts in the field are important factors that can help mitigate this risk. Companies that have had previous success with the FDA or other regulatory agencies also are more attractive than those who may be new to the process. Some accelerated pathways to approval have been put forth such as those outlined in the Orphan Drug Act and the Breakthrough Therapy designation; however, changes in sentiment or perceived safety for pharmaceuticals drugs could change the regulatory environment to demand a more thorough process and these pathways may be extended or additional requirements may be put in place.

Exhibit IX – Success of Phased Trials and Regulatory Approval for Non-New Molecular Entities[43]

Phase	I - Approval	II - Approval	III - Approval	NDA/BLA - Approval
Probability	**13.3%**	**23.2%**	**61.8%**	**91.5%**

Alpha Cognition is advancing its lead candidate under the 505(b)(2) pathway which is generally seen as a lower risk approach to approval. 505(b)(2) is intended for products that have already been approved in another form and it therefore relies on work conducted by the originator. Based on finding provided in the 2021 Clinical Development Success Rates[44] report there is an approximate 15 percentage point benefit in the likelihood of success for a Phase III candidate to advance to an NDA using the 505(b)(2) route versus a new molecular entity (62% vs 47%). Based on this data (see above) we estimate that the average probability of approval for a Phase III candidate traversing the 505(b)(2) route is approximately 62%.

In recent years, contract research organizations (CROs) have taken on a larger role in the development of drug candidates as the complexity and cost of trials has increased. Finding appropriate populations to participate in clin-

[43] Summarized from Clinical Development Success Rates 2011-2020. Compiled by Zacks Analysts.
[44] Summarized from Clinical Development Success Rates 2011-2020. Compiled by Zacks Analysts.

ical trials has become increasingly difficult due to the shift to personalized medicine and orphan indications that address only a small group of patients. This shift has increased the dependence on specialized CROs for project management and clinical monitoring services that add additional risks related to third parties.

Manufacturing is another important component of the drug development process and a critical element of submitting a successful FDA application. Some new drug applicants receive Complete Response Letters (CRLs) related to manufacturing discrepancies and/or insufficient current good manufacturing processes (cGMP). Alpha Cognition has contracted with a manufacturing organization in Taiwan for Alpha-1062, which may make inspections more difficult, especially when travel difficulties related to the pandemic are considered. Acknowledging the risks of a foreign manufacturing location and reliance on a single supplier, the company is seeking backup manufacturers to fill in if the primary provider is unable to meet requirements.

Disruptions due to the coronavirus have been severe throughout the globe and there have been reports of many clinical trials being halted and delayed. Travel restrictions and reallocation of resources may also affect the manufacture and distribution of drug product. Hospitals where clinical trials are conducted are at risk of high demand for services related to the pandemic drawing away resources. The high prevalence of coronavirus infections may dissuade patients from keeping appointments for on-site visits, negatively affecting enrollment and increasing the withdrawal rate.

Drug prices have gained attention as they and other health care costs have risen at a materially faster pace than inflation and wages. As new therapies have been approved, drug prices have increased to reflect higher development costs and improved pricing power of pharmaceutical and biotech companies. On the demand side, deductibles have been steadily increasing over the last decades, and in some cases, individuals and families must cover several thousand dollars in costs before the benefits of insurance begin. Cost sharing or co-insurance is another component of insurance plans that directly increases the burden on patients. This has resulted in greater elasticity in demand for drugs than was previously the case. Individuals with high deductibles or no insurance may be very sensitive to price and avoid treatments with high cost.

While we have discussed a broad variety of risks above, we believe that our forecast parameters, discount rates, success probabilities and valuation metrics address these potential outcomes and our target price reflects an assumption of these risks faced by biotechnology companies.

Peers and Competitors

Alzheimer's and Neurodegenerative Disease

AD is a disease space where there have been few successes over the last decades, and most approved therapies have only been able to address the symptoms of the disease. Multiple categories of agents are in development that seek to slow, stop and reverse AD, including disease modifying, symptomatic and behavioral therapies, each addressing a different component of the disorder. There are many approaches in the disease modifying category with amyloid-β and tau comprising the primary targets along with other efforts addressing inflammation, oxidative stress and synaptic plasticity. Drugs that treat symptoms include cholinesterase inhibitors and glutamate regulators. A combination approach marries these two classes in a product designated memantine, which is approved for moderate-to-severe AD. With respect to non-cognitive symptoms, suvorexant has been approved for insomnia in patients with mild to moderate AD. Another agent named pimavanserin, a serotonin inverse agonist, is under consideration for approval to treat psychosis in AD patients. The most visible approval has been that for Biogen's Aduhelm, which has been controversial given the limited clinical evidence demonstrating effectiveness. Below we summarize details for some of the leading companies and programs in the AD space.

Exhibit X – Peers and Competitors[45]

Ticker	Company	Price	MktCap (MM)	EV (MM)	Drug
ABBV	AbbVie	$150.56	$266,304	$320,663	AL002 mAb in Ph2, AL003 SIGLEC3 in Ph1 (Alector)
ABOS	Acumen Pharma	$5.02	$203	$3	ACU193 Aβ oligomer mAb in Ph1
ACIU	AC Immune	$3.78	$275	$69	Multiple targets in tau & Aβ Ph1 & Ph2
ALEC	Alector	$14.84	$1,217	$482	mAb for AD:TREM2, SIGLEC3, MS4A/progranulin
ALZ	Alzinova AB	4.73 kr	77.3 kr	41.1 kr	mAb, Vaccine & peptide
ANVS	Annovis Bio	$12.41	$101	$54	ANVS401 & 301, oral drug AD, & AD in Down Syn
ATHA	Athira Pharma	$9.17	$343	$107	Small molecule HGF pathway ATH1017 in Ph3 (AD)
AVXL	Anavex Life Sci	$10.37	$790	$639	Ph2/3: ANAVEX2-73, a Σ-1 Receptor
AXSM	Axsome Tx	$29.91	$1,151	$1,085	AXS05:NMDA receptor antagonist/disease agitation
BIIB	Biogen	$209.45	$30,781	$33,253	Aduhelm & other Aβ & tau targets in R&D
BIOA	BioArctic	93.40 kr	8,576 kr	7,690 kr	mAb targeting Aβ oligomer - BAN2401 w/ Eisai
BIVI	BioVie	$3.11	$78	$58	NE3107-TNF-α insulin sensitizer for AD (Ph3)
CGTX	Cognition Thera	$2.51	$55	$132	CT 1812 (σ-2 receptor) in AD & PD
CRTX	Cortexyme	$4.38	$132	$18	Lysine gingipain inhibitor: AD, PD
CYCN	Cyclerion Tx	$1.09	$47	($7)	CY6463 Ph2a AD w/ vascular dementia
ESALY	Eisai	$49.38	$14,644	$12,810	Lecanemab - mAb targeting Aβ
GSK	GlaxoSmithKline	$40.18	$102,129	$124,198	SB-742457, Donepezil, Rosiglitazone, Alector
HLUYY	Lundbeck	$25.26	$5,030	$5,614	Brexpiprazole: AD agitation Ph3
INMB	INmune Bio	$7.79	$139	$69	Mild AD & MCI soluble TNF/inflammation target
JNJ	Janssen subsidiary	$169.48	$445,608	$443,985	JNJ-63733657, ACI-35 with ACIU
LGVN	Longeveron	$6.16	$121	$102	Cell therapy for AD: Lomecel-B/Ph2a
LLY	Eli Lilly	$262.87	$250,343	$261,781	Solanezumab, donanemab - mAb targeting Aβ
LLY	Prevail Tx	$262.87	$250,343	$261,781	Gene therapy for neurodegen disease (PD/FTD)
MOR	MorphoSys	$6.10	$835	$693	Gantenerumab w/ Roche (Ph3)
NGENF	NervGen Pharma	$1.57	$72.4	$67.1	PTPσ modulator (NVG291) preclin for AD
PASG	Passage Bio	$2.93	$159	($196)	Gene therapy-progranulin
ARFXF	ProMIS Neurosciences	$0.11	$48	$31	PMN310 targeting Aβ oligomers
RHHBY	Roche	$46.04	$314,453	$317,785	Semorinemab (tau), gantenerumab (Aβ)
SAVA	Cassava Sciences	$37.31	$1,493	$1,252	Simufilam for AD/SavaDx diagnostic for AD
SIOX	Sio Gene Tx	$0.59	$43.4	($30)	Gene therapy for neurodegen disease (PD)
SNPX	Synaptogenix	$6.64	$44	$13	Bryostatin-1 restorative therapy for AD
TAK	Takeda	$15.05	$47,626	$78,250	DNL919 ATV targeting TREM2 with Denali
pvt	AgeneBio				AGB101: SV2A synaptic vesicle protein in Ph2b
pvt	EIP Pharma				Oral p38 α-inhibitor neflamapimod Ph3 ready
pvt	Elixiron				EI-1071 for AD and cancer programs
pvt	TauRx Therapeutics				TRx-5 & -15/Tau Aggregation Inhibitor
ACOGF	Alpha Cognition	$0.77	$34.6	$30.9	A1062 for AD & TBI/A0602 progranulin for ALS

[45] Price and market capitalization data is as of March 4, 2022

Valuation

Alzheimer's Disease is the seventh leading cause of death in the United States; however, in contrast to heart disease and cancer, its prevalence has increased materially over the last decades. With US and global populations increasing in average age, we expect AD to continue to dominate the health care landscape and further increase costs of treatment and caregiver obligations. With no clinically proven disease modifying therapy available, attention shifts towards treatments that can improve symptoms and preserve physical and cognitive function. While existing symptomatic treatments are able to address many of AD's burdens, side effect profiles limit usage and call for a better approach. With Alpha Cognition's prodrug formulation of galantamine, many of the GI-related issues may be resolved allowing patients to better adhere to treatment. With this benefit, patients should experience more stable cognition, greater independence and lower risk of death. Caregivers may also experience improved quality of life and reduced burden as patients exhibit improved behavioral symptoms and are better able to care for themselves.

If successfully approved, Alpha-1062 will be commercialized in the United States with sales efforts targeting neurology and long-term care physicians. The company intends to develop its own sales force in the US and partner with distributors for sales outside of the United States.

Based on the company's intent, our valuation examines the opportunity for Alpha-1062 in both the US and developed regions, which includes Europe, Latin America and Asia. We conservatively estimate a 2022 submission of an NDA in the US and partner regulatory submissions in foreign territories in 2023. Approval is anticipated in 2023 for the US and in 2024 in foreign jurisdictions. First sales are modeled to begin in 2024 in the US and in 2025 elsewhere. While this assumes commercialization to begin a year later than company guidance, we believe that this conservatively allows for any unexpected regulatory or manufacturing delays.

In the United States, we estimate an AD population of 6.3 million in 2022, growing at a 2.5% annual rate.[46] The addressable market for Alpha-1062 is in mild to moderate AD, which comprises about 80% of the total population. In 2024 this is estimated to be approximately 5.3 million in the US. We assume a modest 15 basis points of penetration in the first year of commercialization growing to 100 basis points by 2029. While patent protection could extend further, we estimate that in 2031 market share will be cut to 50 basis points and then persist at 20 basis points over the next decade. Annual treatment cost is estimated at $5,700 in 2024 growing at a 3% annual rate. These assumptions generate $46 million of revenues in 2024 growing to a peak of $424 million by 2030 and declining thereafter.

In the rest of the developed world, we estimate an AD population of 32 million in 2022 growing at a 2.5% annual rate with approximately 80% of the population in the addressable mild to moderate group. In 2025, the first year of commercialization for Alpha-1062, this is approximately 27.8 million. First year penetration into the addressable market is forecast at 8 basis points rising to 35 basis points by year five. After 2031, penetration rates are expected to taper off by over half. Pricing in ex-US regions is forecast to be 45% of US levels or $2,700 per year of treatment growing at a 3% annual rate in 2025. We anticipate that Alpha Cognition will partner with others for international distribution and that economic value paid will consist of upfronts, milestones and royalties. For simplicity we assume that all economic value received from distributors is represented by a 33% royalty. Total revenues in year one are forecast at $59 million rising to a peak of $321 million by year five. Royalty revenues are forecast at $19 million rising to a peak of $125 million by year eight. After the end of patent protection, a 15 basis point penetration rate will persist in our model.

Cost of goods sold is expected to be approximately 10% of revenues, which consists of a small royalty, the costs of manufacturing and packaging. Sales and marketing is estimated to be 30% of direct sales revenues. Research and development cost is modeled at $8.2 million in 2022, falling to $8.0 million in 2023 and $5.0 million in 2024. After 2024, we do not recognize any R&D expense as the model does not include costs or contributions for other programs.[47] General and administrative expense is estimated at $4.5 million in 2022, and rising thereafter at approximately 3% per year. Sales and Marketing expense is calculated at 30% of domestic sales revenues. Taxes, which include both federal and local rates are modeled at 25%

[46] Our annualized growth rate is based on forecasts of 12.7 million with AD by 2050 estimated by the Alzheimer's Association.
[47] We will add the costs and benefits of additional programs to our model when the company can be reasonably expected to advance the indications and when clinical trials have a reasonable expectation of starting.

We use a discounted cash flow (DCF) model to estimate the valuation of Alpha Cognition. A discount rate of 15% is applied to cash flows from 2022 to 2042 after which a terminal growth rate of -10% is applied. We probability-adjust the likelihood of success for the Alpha-1062 program and apply a 62% estimated rate of success based on other Phase III programs using the 505(b)(2) pathway. Shares outstanding used for calculating our valuation include the 60.6 million shares outstanding as of January 2022 along with 44.5 million other shares from warrants, options, restricted shares, preferred shares and performance shares. We also anticipate that the company will raise an additional amount of capital of an estimated $20 million in proceeds from the issuance of 20 million shares at $1.00 per share that will add additional shares to the outstanding balance. The sum of all of these claims on equity equates to approximately 125 million shares. The result of our work generates a valuation of $2.75 per share.

CONCLUSION

Alpha Cognition has applied a prodrug and salt modification to generic galantamine in an effort to improve the side effect profile of this useful AChEI. Galantamine has demonstrated the ability to improve cognition, reduce severe dementia, improve behavioral symptoms and improve the burden of caregivers in a variety of studies conducted over the last two decades. One of the shortcomings of galantamine and other AChEIs has been the side effect profile which leaves patients suffering from a variety of GI-related issues including nausea, vomiting, weight loss and dizziness. With its prodrug formulation, Alpha Cognition's Alpha-1062 offers an alternative that can achieve many of the benefits of galantamine without the side effects. Galantamine itself offers other benefits relative to competing AChEIs related to its dual mechanism of action and absence of insomnia. The dual mechanism of action both prevents the breakdown of ACh and enhances the sensitivity of nAChRs.

Alpha-1062 is now being investigated in Phase III study which is expected to read out trial results in second quarter 2022, followed by an NDA submission in third quarter 2022. Assuming acceptance and normal review time by the FDA, approval for Alpha-1062 may arrive by late 2023. We take a conservative stance in our estimates and assume that first sales take place in 2024. Alpha Cognition plans to develop its own sales force for commercialization in the United States and partner with distributors outside of the US. With a potentially superior product both in terms of efficacy and safety; and based on our pricing and penetration estimates, Alpha-1062 could generate revenues of several hundred million dollars per year.

In addition to the lead indication in AD, Alpha Cognition is also working on treatments for mild traumatic brain injury, and a combination therapy including memantine for Alpha-1062. The company also offers a gene therapy approach for amyotrophic lateral sclerosis (ALS) which seeks to increase the level of progranulin in the brain. While these programs are now at a preclinical stage, they will soon be ready for clinical development.

Alpha Cognition is able to take advantage of several favorable regulatory provisions including 505(b)(2) for new formulations of previously approved drugs and the orphan drug designation for ALS. These approaches will lower development cost and accelerate timelines providing a favorable reward to risk if approved. We initiate Alpha Cognition with a $2.75 valuation.

Key reasons to own Alpha Cognition shares:

- **Attractive indications with material unmet need**
  - **Alzheimer's Disease (AD)**
  - **Traumatic Brain Injury (TBI)**
  - **Amyotrophic Lateral Sclerosis (ALS)**
- **Galantamine is the active metabolite of Alpha-1062**
  - **Can significantly slow AD & reduce all-cause mortality**
  - **Shorter titration schedule providing faster onset of action**
  - **Differentiating beneficial effects on nicotinic receptor**
  - **Addresses GI side effects through prodrug formulation**
  - **Low rates of insomnia vs. other AChEIs**
  - **Considered a new chemical entity (NCE)**
- **Modulates multiple receptors for synergistic effect**
  - **Binding to AChE allows for greater amounts of ACh to persist**
  - **Binding to nAChR enhances the signal from ACh**
- **505(b)(2) Regulatory Pathway for Alpha-1062**
  - **Abbreviated Route to Approval**
  - **Lower Cost**
  - **Allows use of innovator safety and efficacy information**
- **Progranulin gene therapy program**
  - **Pursuing indication in amyotrophic lateral sclerosis (ALS)**
  - **Mammal data available in 1Q:22**

PROJECTED FINANCIALS

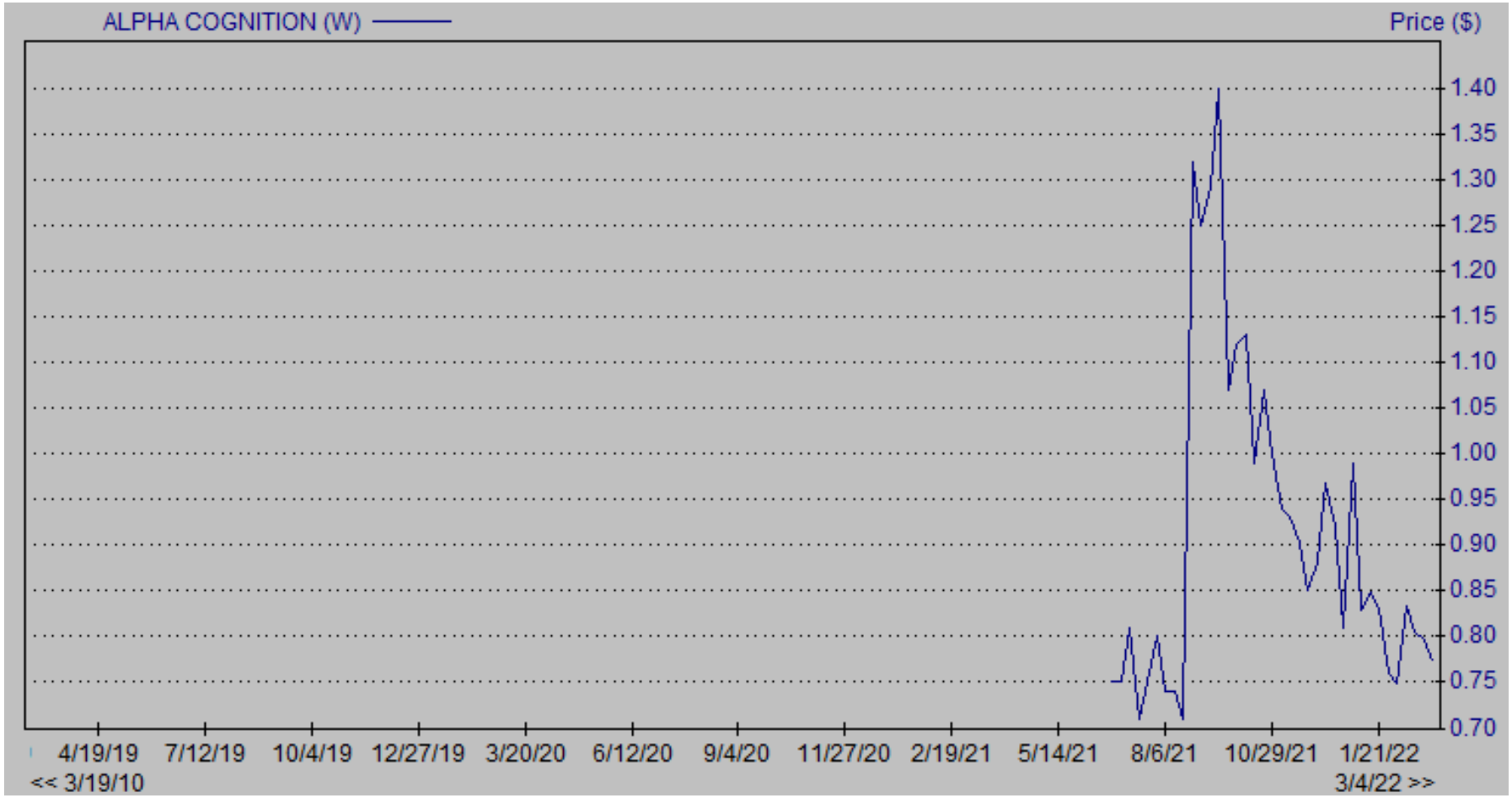
Alpha Cognition Inc. - Income Statement

Alpha Cognition Inc.	2020 A	Q1 A	Q2 A	Q3 A	Q4 E	2021 E	2022 E	2023 E
Total Revenues ($US '000)	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth								
Research & Development	$4,673	$1,622	$1,528	$2,140	$2,200	$7,491	$8,200	$5,000
General & Administrative	$1,803	$834	$704	$980	$1,100	$3,618	$4,500	$4,600
Income from operations	($6,476)	($2,456)	($2,233)	($3,120)	($3,300)	($11,109)	($12,700)	($9,600)
Operating Margin								
Other Items	$691	($9,769)	$2,387	($1,169)	$0	($8,551)	$0	$0
Pre-Tax Income	($5,784)	($12,225)	$154	($4,289)	($3,300)	($19,660)	($12,700)	($9,600)
Provision for Income Tax	$0	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0.0%*							
Net Income	**($5,784)**	**($12,225)**	**$154**	**($4,289)**	**($3,300)**	**($19,660)**	**($12,700)**	**($9,600)**
Net Margin	0%							
Reported EPS	**($0.13)**	**($0.28)**	**$0.00**	**($0.09)**	**($0.06)**	**($0.41)**	**($0.20)**	**($0.14)**
YOY Growth								
Basic Shares Outstanding	42,947	44,373	47,445	45,978	52,500	47,574	63,000	68,000

Source: Company Filing // Zacks Investment Research, Inc. Estimates

HISTORICAL STOCK PRICE

Alpha Cognition Inc. – Share Price Chart[48]



[48] Source: Zacks Research System

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