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Tiziana Life Sciences PLC (TLSA: NASDAQ)

TLSA: IND Cleared by FDA and Alzheimer's Deep Dive

Research Note

Tiziana Life Sciences PLC (NASDAQ: TLSA) announced the clearance of its Investigational New Drug (IND) application for its anti-CD3 foralumab in Alzheimer's Disease (AD) in an August 15th press release. Foralumab is now the subject of a Phase II clinical trial in AD building on other work being done in an ongoing non-active secondary progressive multiple sclerosis (na-SPMS) study.

Foralumab safety work has already been completed to prepare it for other indications; therefore, following the IND clearance Tiziana may to launch a Phase II exploratory trial. According to the company's scientific advisor, Dr. Howard Weiner, screening is expected to begin in the fall with first enrollment expected by the beginning of 2024. Results from the trial could be available by the fall of 2024. Brigham and Women's Hospital will oversee the trial with additional details expected to be shared on clinicaltrials.gov in coming weeks.

Dr. Weiner highlighted the drivers of AD: beta amyloid (βA), tau and inflammation. Two products have recently been approved to address beta amyloid (Aduhelm and Leqembi); however, there are none specifically approved to address tau and inflammation. Tiziana's anti-CD3 monoclonal antibody has demonstrated the ability to address inflammation[1] and may be not only improve the condition in AD patients but also address some of the side effects of beta amyloid therapies such as cerebral edema.

Alzheimer's Disease

Alzheimer's Disease (AD) was the seventh most common cause of death in the United States in 2021[2] 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 strongly effective disease modifying therapy has eluded medicine; nevertheless, there are symptomatic treatments available for AD and new formulations may improve their safety and efficacy. Two classes of symptomatic treatment include acetylcholinesterase inhibitors (AChEIs), N-methyl-D-aspartate (NMDA) receptor antagonists and beta amyloid therapies.

Alzheimer's Disease (AD) is a neurodegenerative condition which affects almost seven million Americans[3] and over 30 million people worldwide.[4] Due to faster growth in 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%.

[1] Moreira, T.G. *et al*. Nasal administration of anti-CD3 mAb (Foralumab) downregulates NKG7 and increases TGFB1 and GIMAP7 expression in T cells in subjects with COVID-19. Proceedings of the National Academy of Sciences, March 2023.
[2] Centers for Disease Control and Prevention, National Center for Health Statistics, Leading Causes of Death.Accessed August 2023.
[3] Alzheimer's Association Facts and Figures. Accessed August 2023.
[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

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 βA 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 exhibit 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 for death. 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 mortality, AD 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 $340 billion for unpaid caregivers representing over 18 billion hours of service in 2023.[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 greater.

[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
[8] Alzheimer's Association Factsheet. 2023 Alzheimer's Disease Facts and Figures.
[9] Alzheimer's Association Factsheet. 2021 Alzheimer's Disease Facts and Figures.

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.

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 used 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.

[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.

Treatment

Acetylcholinesterase Inhibitors (AChEI) and N-methyl-D-aspartate (NMDA) Receptor Antagonists
There are several medicines available that will treat the symptoms of AD. There are five approved 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. 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 and Lecanemab
The first new drug to be approved for AD in almost 20 years came to market in 2021. Aducanumab followed a tortuous path full of ups and downs prior to the FDA's June 2021 approval. The beta-amyloid removing therapy was branded Aduhelm. 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. Following approval, uptake of the drug was weak especially after Medicare decided to only cover the drug for individuals enrolled in a clinical trial.

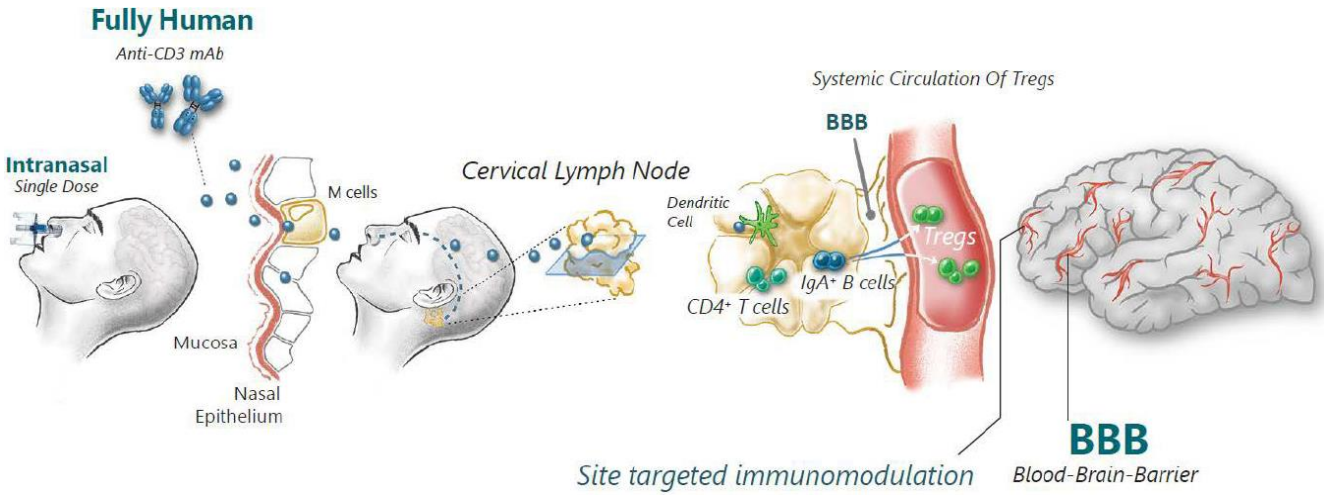
In July 2023, the FDA approved the second beta-amyloid drug for AD, lecanemab or Leqembi as it is branded by Eisai and Biogen. Data for lecanemab was better than that for aducanumab showing a reduction in amyloid plaques and a slowing in cognitive decline. Side effects for lecanemab were also improved over aducanumab as the former showed lower rates of brain swelling and microhemorrhage.

Another in-development amyloid-beta focused product is Eli Lilly's donanemab which has shown impressive results in slowing cognitive decline. The candidate met primary and secondary endpoints in its pivotal trial and has been submitted to the FDA in a biologics license application (BLA) which should receive a response from the agency before year end 2023.

Alzheimer's Disease (AD) Presentation

Dr. Howard Weiner, the chairman of Tiziana's scientific advisory board, presented research at the International Conference on Alzheimer's and Parkinson's Disease and Related Neurological Disorders (ADPD) Conference on April 1, 2023. ADPD was held in Gothenburg, Sweden. Dr. Weiner is a close collaborator with Tiziana on anti-CD3 therapies, a Co-Director of the Ann Romney Center for Neurologic Diseases at Brigham and Women's Hospital and a founding member of Mass General Brigham. The title of Dr. Weiner's lecture was Immunotherapy of Alzheimer's Disease by Modulation of Innate Immunity.

Exhibit II – Intranasally-Administered Foralumab for Neurodegenerative Diseases[14]



[14] Source: Tiziana Corporate Presentation, January 2023

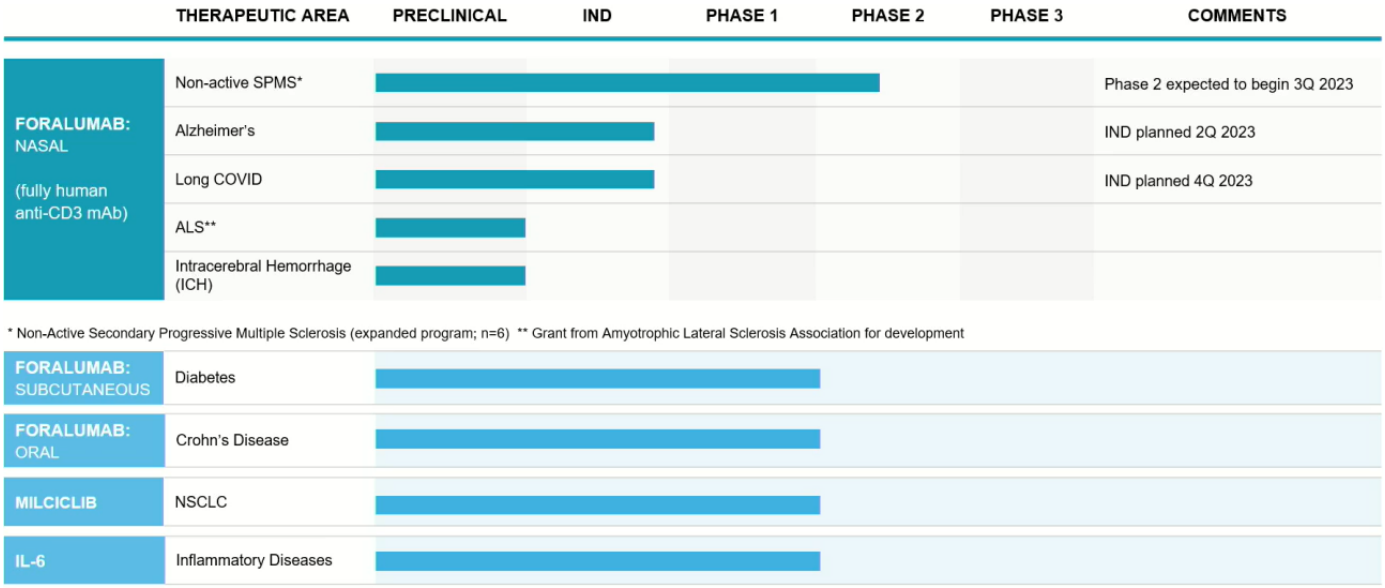
The data presented, which is related to the effect of anti-CD3 in a rodent model, demonstrated the reduction of microglia activation and behavior improvement in rodent models of AD. Dr. Weiner hypothesized that the modulation of innate immunity via targeting microglia will play a synergistic role with approved anti-amyloid Alzheimer's treatments, which include lecanemab and aducanumab. Research has shown that intranasal rodent anti-CD3 mAb and intranasal fully human anti-CD3 mAb (foralumab) will decrease microglia activation in rodents and humans. Foralumab's mechanism of action, which reduces inflammation, appears to be complementary to the beta-amyloid sequestration mechanism of the approved biologics in animal models.

Tiziana is applying for and expects to receive $3 million of non-dilutive funding from an undisclosed Alzheimer's foundation. The funds will support the recently cleared Phase IIa trial. The application for the grant was targeted for 2Q:23 with a response expected in 3Q:23. The study will evaluate the outcomes related to microglial activation for three months of intranasal foralumab administration. Endpoints will determine whether or not Tiziana's candidate can reduce neuroinflammation triggered by beta-amyloid plaque and return activated microglia to a baseline homeostatic state.

Milestones

- Filing of IND for foralumab in AD – 3Q:23
- AD IND clearance – August 2023
- Begin Alzheimer's Phase II trial – 4Q:23
- Results from initial AD clinical study – 2H:24

Exhibit III – Tiziana Development Pipeline[15]



Summary

Tiziana received FDA clearance for a Phase II clinical trial in Alzheimer's Disease and is expected to prepare to start the trial this fall and enroll first patients after the beginning of the year. There are many causes behind AD and a multimodal approach is likely necessary to be effective. There are a few beta-amyloid therapies approved and other candidates in development to address tau and inflammation. Tiziana's foralumab may be able to address the inflammation component of AD and has shown efficacy in the human CNS in the multiple sclerosis trial. Now that the IND has been cleared for Alzheimer's disease, preparations to start the trial will begin with the first enrollee expected in early 2024. In this note, we provide background on AD with a review of the disease epidemiology, etiology and existing therapies. It closes with a review of Dr. Weiner's AD presentation in Sweden and a summary of milestones expected in the AD development program.

[15] Source: Corporate presentation, KOL Webinar, June 5, 2023.

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