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Rating	Buy
Price (07/21/2025)	$1.62
Price Target	$8.00

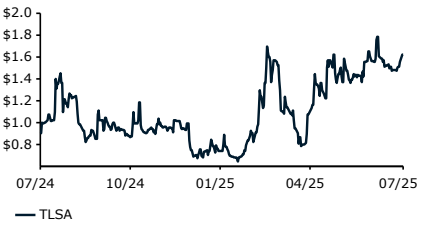
Market Data

% to Target	393.8%
52-Week High	1.91
52-Week Low	0.63
Market Cap (mil)	189.3
Cash & Equivalents	$3.7
Total Debt	$0.0
Enterprise Value	$185.6
Cash per Share	$0.03
Shares Outstanding (mil)	116.9
3-Month ADTV	317,983
Short interest (mil)	NA
Float	62.1
Fiscal Year-End	Dec

Estimates

FY	**2024A**	**2025E**	**2026E**
EPS Diluted	(0.11)	(0.18)	(0.20)
Revenue ($M)	0.0	0.0	0.0

Performance Chart



Tiziana Life Sciences Ltd (TLSA)

Creating the "Humira" for CNS Diseases — Initiating Coverage with $8 PT

KEY POINTS

Initiating coverage of Tiziana Life Sciences, Ltd. (TLSA) with a Buy rating and an $8/share 12-month price target. Tiziana is developing an intranasal antibody for numerous central nervous system (CNS) conditions, aspiring to achieve a similar success to Humira in inflammatory disease.

Our Buy thesis on the shares of Tiziana is based on the following:

The company is building a neurological franchise with foralumab that could be analogous to AbbVie's (ABBV; Not Rated) Humira, that achieved peak sales of $20B+ with approval for nine different inflammatory conditions.

Immune Modulation with Convenience: Intranasal foralumab is a novel, non-invasive anti-CD3 monoclonal antibody therapy targeting immune dysregulation in diseases, such as MS, Alzheimer's, and ALS. Delivered via the nasal route, it modulates the mucosal immune system to enhance regulatory T cell responses and reduce inflammation — avoiding systemic immune suppression or cytokine storms. Early studies show it promotes immune tolerance rather than widespread systemic activation.

Clinical Evidence: In a `10-patient,` non-active Secondary Progressive MS (SPMS) trial, nasal foralumab halted disability progression over six months, with no worsening. Three of four patients had improved at the 12-month time point, which would indicate that long-term use of the drug will not only halt progression, but may reverse neurological decline. Six patients reported clinically meaningful reductions in fatigue, which correlated with baseline hippocampal microglial activity. PET imaging showed significant declines in microglial activation after six months, and MRI detected no new lesions, suggesting the therapy stabilized disease and reduced neuroinflammation.

An IV drug, ocrelizumab - indicated for the **active** form of SPMS - achieved $8.4B in sales in 2024.

Broadening: Tiziana has begun to explore foralumab in randomized, placebo controlled trials, not only in MS, but in Alzheimer's and ALS with consideration of further neurological indications. While we only ascertain the market potential of the MS indication, the development timeline could potentially be faster in ALS.

Blockbuster Potential: No current drugs specifically target **non-active** SPMS. If approved, intranasal foralumab may justify a premium price — estimated at $85,000 annually. With a pending CNS-use patent would expire in 2043, the drug could have a 14-year commercial window. Assuming US approval and launch in 2029 and EU5 in 2030, and capturing up to 50% market share, projected net sales could reach $1.6B in the US and $1B in EU5 countries.

Valuation & Risks: We arrive at our 12-month price target of $8 per share by assessing the after-tax, risk-adjusted NPV of potential future cash flows from foralumab in non-active SPMS. The probability-adjusted (45%), fully taxed (21%) NPV at a 15% discount rate of potential cash flows until 2043 is approximately $1.2B, equivalent to $8 per share, corresponding to our 12-month price target. Potential factors that could prevent shares from reaching our price target include the failure of foralumab to demonstrate significant efficacy benefits or being

deemed unsafe, leading to the discontinuation of clinical programs and commercial launch. In addition, the company may not be able to raise additional funds to complete development.

BACKGROUND

Multiple Sclerosis Overview

Multiple Sclerosis (MS) is a chronic, immune-mediated disorder that targets the central nervous system (CNS), specifically the brain, spinal cord, and optic nerves[1]. The disease arises when the immune system mistakenly attacks the myelin sheath — the protective layer around nerve fibers — resulting in demyelination, inflammation, and eventual neurodegeneration. These attacks disrupt communication between the brain and the rest of the body, leading to a wide array of neurological symptoms. MS is a heterogeneous disease with variable courses, including periods of relapse and remission or steady progression of symptoms over time.

Clinical manifestations of MS vary widely depending on the location of CNS involvement. Common symptoms include visual disturbances like optic neuritis, muscle weakness, coordination problems, numbness, tingling, fatigue, and cognitive impairments. Many patients also experience bladder or bowel dysfunction, mood disorders such as depression, and chronic pain. These symptoms can fluctuate in severity and often significantly impair daily functioning and quality of life.

Prevalence and Risk Factors. MS is increasingly recognized as a global disease affecting approximately 2.8 million people worldwide[2]. In the US, it is currently estimated to affect between 300,000 and 400,000 people[3]. Historically, MS prevalence has been higher in regions farther from the equator, with a clear latitudinal gradient linked to lower exposure to UVB radiation, which is necessary for the body to produce vitamin D. MS is also significantly more common in women, with a female-to-male ratio nearing 3:1 in developed nations, a marked increase from the near-equal ratio seen in the early 1900s. Additionally, exposure to organic solvents and smoked (but not oral) tobacco has been associated with MS, possibly due to immune-related modifications triggered in the lungs through antigen presentation mechanisms.

Etiology. The exact cause of MS remains unclear, but researchers widely agree that its development involves a complex interaction of immune, environmental, and genetic factors[4]. Among these, the leading theory suggests that MS is an autoimmune disease, in which the body's immune system mistakenly targets CNS. The "outside-in" hypothesis proposes that external antigens activate proinflammatory CD4+ T cells—specifically Th1 and Th17 cells—which then migrate across the blood-brain barrier and initiate an immune response against CNS tissues through molecular mimicry or cross-reactivity[5]. Alternatively, the "inside-out" model suggests that MS may begin with an internal CNS defect that triggers immune-mediated inflammation and damage.

Environmental factors have long been suspected to influence MS risk. A notable observation is the latitudinal gradient in MS prevalence, with higher rates in populations living farther from the equator, which has been linked to vitamin D deficiency due to reduced ultraviolet B (UVB) exposure. Low vitamin D levels—either from limited sun exposure, poor dietary intake, or genetic factors affecting vitamin D metabolism—may increase susceptibility to MS[6]. Infections, particularly with the Epstein-Barr virus (EBV), have also been implicated in triggering MS, although the exact mechanism remains under investigation[7]. These environmental elements likely interact with a person's genetic makeup to influence the risk and course of the disease.

Genetic predisposition is another important contributor to MS[8]. Individuals with a first-degree relative who has MS face a 2–4% lifetime risk of developing the disease, compared to 0.1% in the general population. The risk is even higher among monozygotic twins (20–30% concordance) than dizygotic twins (around 5%) or parent-child pairs (about 2%). These patterns indicate a genetic influence, though no single gene is responsible. Rather, MS is believed to be polygenic, with contributions from numerous gene variants.

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[1] Dobson R, Giovannoni G. Multiple sclerosis - a review. *Eur J Neurol.* 2019 Jan;26(1):27-40. doi: 10.1111/ene.13819. Epub 2018 Nov 18. PMID: 30300457.
[2] Walton C, King R, Rechtman L, Kaye W, Leray E, Marrie RA, Robertson N, La Rocca N, Uitdehaag B, van der Mei I, Wallin M, Helme A, Angood Napier C, Rijke N, Baneke P. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. *Mult Scler.* 2020 Dec;26(14):1816-1821. doi: 10.1177/1352458520970841. Epub 2020 Nov 11. PMID: 33174475; PMCID: PMC7720355.
[3] Wallin MT, Culpepper WJ, Campbell JD, Nelson LM, Langer-Gould A, Marrie RA, Cutter GR, Kaye WE, Wagner L, Tremlett H, Buka SL, Dilokthornsakul P, Topol B, Chen LH, LaRocca NG; US Multiple Sclerosis Prevalence Workgroup. The prevalence of MS in the United States: A population-based estimate using health claims data. Neurology. 2019 Mar 5;92(10):e1029-e1040. doi: 10.1212/WNL.0000000000007035. Epub 2019 Feb 15. *Erratum in: Neurology.* 2019 Oct 8;93(15):688. doi: 10.1212/WNL.0000000000007915. PMID: 30770430; PMCID: PMC6442006.
[4] Tafti D, Ehsan M, Xixis KL. Multiple Sclerosis. [Updated 2024 Mar 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499849/
[5] Tsunoda I, Fujinami RS. Inside-Out versus Outside-In models for virus induced demyelination: axonal damage triggering demyelination. *Springer Semin Immunopathol.* 2002;24(2):105-25. doi: 10.1007/s00281-002-0105-z. PMID: 12503060; PMCID: PMC7079941.
[6] Sintzel MB, Rametta M, Reder AT. Vitamin D and Multiple Sclerosis: A Comprehensive Review. *Neurol Ther.* 2018 Jun;7(1):59-85. doi: 10.1007/s40120-017-0086-4. Epub 2017 Dec 14. PMID: 29243029; PMCID: PMC5990512.
[7] Guan Y, Jakimovski D, Ramanathan M, Weinstock-Guttman B, Zivadinov R. The role of Epstein-Barr virus in multiple sclerosis: from molecular pathophysiology to in vivo imaging. *Neural Regen Res.* 2019 Mar;14(3):373-386. doi: 10.4103/1673-5374.245462. PMID: 30539801; PMCID: PMC6334604.
[8] Westerlind H, Ramanujam R, Uvehag D, Kuja-Halkola R, Boman M, Bottai M, Lichtenstein P, Hillert J. Modest familial risks for multiple sclerosis: a registry-based study of the population of Sweden. *Brain.* 2014 Mar;137(Pt 3):770-8. doi: 10.1093/brain/awt356. Epub 2014 Jan 17. PMID: 24441172; PMCID: PMC3927700.

Standard of Care for MS

The current standard of care for MS focuses on three major areas: disease-modifying therapies (DMTs), symptomatic treatment, and relapse management. DMTs aim to reduce the frequency and severity of relapses and slow disease progression. These include injectable agents like interferon beta and glatiramer acetate, oral drugs such as fingolimod and dimethyl fumarate, and monoclonal antibodies like natalizumab and ocrelizumab. Symptomatic treatments target individual symptoms such as spasticity, fatigue, and pain, while relapses are typically managed with high-dose corticosteroids or plasma exchange. In addition, rehabilitation and supportive care, including physical therapy and psychological support, are essential components of long-term management.

Despite advancements, current treatments have notable limitations. Most therapies are not curative and cannot reverse existing neurological damage. Their effectiveness in progressive forms of MS, particularly primary and secondary progressive MS, remains limited. Additionally, many DMTs are associated with significant side effects, including increased risk of infections and malignancies due to immunosuppression. Treatment response varies greatly among individuals, and a personalized medicine approach is still under development. High costs and limited global access further complicate management. Finally, delays in diagnosis and a lack of effective neuroregenerative therapies highlight the ongoing unmet needs in MS care.

In summary, MS is a complex and often debilitating neurological disease. While the therapeutic landscape has significantly improved, particularly for relapsing forms, there remains a pressing need for safer, more effective treatments—especially for progressive MS—and for strategies that repair or restore damaged neural tissue.

Clinical Stages and Manifestations

Clinically Isolated Syndrome (CIS)

MS typically begins between the ages of 20 and 40. Clinically isolated syndrome (CIS) is considered the earliest clinical manifestation suggestive of MS[9] (Figure 1). It refers to a first episode of neurological symptoms caused by inflammation and demyelination in the CNS, lasting at least 24 hours, and occurring in the absence of fever, infection, or other underlying causes[10]. CIS can affect various parts of the CNS, leading to symptoms such as optic neuritis (blurred or lost vision in one eye), brainstem dysfunction (e.g., double vision, vertigo), or partial transverse myelitis (numbness, weakness, or paralysis).

The clinical significance of CIS lies in its potential to progress to multiple sclerosis, especially when MRI findings show evidence of demyelinating lesions in the brain or spinal cord. Patients with CIS and MRI lesions typical of MS are at a higher risk of developing clinically definite MS (CDMS). In contrast, patients without such MRI abnormalities have a lower risk of conversion, though they still require monitoring.

CIS is a pivotal concept in early MS diagnosis, and current diagnostic criteria allow for a diagnosis of MS to be made even after a single clinical event if dissemination in space and time is demonstrated via MRI or CSF markers. This enables early intervention with DMTs, which can reduce the risk of a second attack and slow disease progression. Several studies have shown that early treatment of CIS with DMTs such as interferon-beta or glatiramer acetate significantly reduces the rate of conversion to MS.

CIS is a warning sign of possible MS and represents a critical window for early diagnosis and treatment. While not all patients with CIS will go on to develop MS, close monitoring and prompt imaging are essential to determine prognosis and guide management.

[9] Efendi H. Clinically Isolated Syndromes: Clinical Characteristics, Differential Diagnosis, and Management. *Noro Psikiyatr Ars.* 2015 Dec;52(Suppl 1):S1-S11. doi: 10.5152/npa.2015.12608. Epub 2015 Dec 1. PMID: 28360754; PMCID: PMC5353226.
[10] Filippi M, Bar-Or A, Piehl F, Preziosa P, Solari A, Vukusic S, Rocca MA. Multiple sclerosis. *Nat Rev Dis Primers*. 2018 Nov 8;4(1):43. doi: 10.1038/s41572-018-0041-4. Erratum in: Nat Rev Dis Primers. 2018 Nov 22;4(1):49. doi: 10.1038/s41572-018-0050-3. PMID: 30410033.

Relapsing-Remitting MS (RRMS)

Relapsing-Remitting MS is the most common initial diagnosis, marked by episodic attacks followed by partial or full recovery[11]. Approximately 85% of people with MS are initially diagnosed with RRMS. It is characterized by episodes of new or worsening neurological symptoms (relapses), followed by periods of partial or complete recovery (remissions).

RRMS is characterized by clearly defined episodes of new or worsening neurological symptoms, known as relapses or flare-ups, followed by periods of remission where symptoms partially or completely improve[12]. The course of RRMS can vary significantly between individuals, but the hallmark feature is the episodic nature of the disease, with periods of stability between attacks.

The symptoms of RRMS depend on the location and extent of inflammation and demyelination in the CNS. One of the most frequent early signs is optic neuritis, which causes pain with eye movement and blurred or decreased vision, often in one eye. Some patients may experience double vision or involuntary eye movements (nystagmus) due to brainstem involvement. Sensory disturbances are also common, including numbness, tingling, or a “pins and needles” sensation, typically in the limbs, trunk, or face. A classic symptom called Lhermitte’s sign, described as an electric-shock sensation running down the spine when bending the neck, may also occur.

Motor symptoms often manifest as weakness, usually in the arms or legs, and may be accompanied by spasticity, which is involuntary muscle stiffness or cramping. Coordination problems, unsteady walking (ataxia), and tremors can develop as the disease affects the cerebellum or spinal cord. Fatigue is one of the most debilitating and persistent symptoms in RRMS, often out of proportion to activity and not relieved by rest.

Bladder and bowel dysfunction can also occur, including urinary urgency, incontinence, hesitancy, and constipation. In some cases, bowel incontinence may develop. Many individuals with RRMS experience cognitive symptoms, such as difficulties with memory, attention, and processing speed. Emotional disturbances like depression, anxiety, and mood swings are also common and can significantly impact quality of life. Additionally, sexual dysfunction—including reduced libido or erectile difficulties in men—is frequently reported but often underdiscussed.

As RRMS progresses, individuals may recover completely from relapses early in the course of the disease. However, over time, the damage can accumulate, and residual symptoms may persist even after remission. This progressive burden of neurological impairment underscores the importance of early diagnosis and intervention.

Progressive MS

In many patients, RRMS eventually evolves into secondary progressive MS (SPMS), which is defined by a gradual and continuous decline in neurological function, often occurring independently of relapses. Primary Progressive MS (PPMS), in contrast, involves gradual symptom progression from onset without clear relapses. PPMS and SPMS share a common feature: a steady, long-term worsening of neurological function. However, they differ significantly in how they begin and how the disease progresses.

PPMS is characterized by a gradual onset of symptoms from the very beginning, without any initial relapses or periods of remission. Patients with PPMS typically experience a slow but continuous accumulation of disability, often focused in one primary neurological domain, such as motor function or gait. Unlike RRMS, there are no distinct attacks or recovery periods. Inflammatory activity on MRI—such as contrast-enhancing lesions—is less common in PPMS compared to other MS types, reflecting its stronger association with neurodegeneration rather than inflammation. PPMS tends to be diagnosed later in life, often around age 40, and it affects men and women equally.

In contrast, SPMS develops after an initial RRMS phase, during which patients experience clear relapses (episodes of new or worsening neurological symptoms) followed by periods of partial or full recovery. Over time, typically after 10 to 15 years, the disease transitions into SPMS, marked by steady progression of disability that can occur with or without continued relapses or MRI activity. This shift to progressive decline is often difficult to pinpoint and is usually diagnosed retrospectively, after clinicians observe sustained worsening of neurological function. While SPMS shares features of progression with PPMS, it

[11] Niino M, Miyazaki Y. [Relapsing-Remitting Multiple Sclerosis]. *Brain Nerve*. 2021 May;73(5):442-449. Japanese. doi: 10.11477/mf.1416201784. PMID: 34006674.
[12] Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS, Thompson AJ, Wolinsky JS, Balcer LJ, Banwell B, Barkhof F, Bebo B Jr, Calabresi PA, Clanet M, Comi G, Fox RJ, Freedman MS, Goodman AD, Inglese M, Kappos L, Kieseier BC, Lincoln JA, Lubetzki C, Miller AE, Montalban X, O'Connor PW, Petkau J, Pozzilli C, Rudick RA, Sormani MP, Stüve O, Waubant E, Polman CH. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology.* 2014 Jul 15;83(3):278-86. doi: 10.1212/WNL.0000000000000560. Epub 2014 May 28. PMID: 24871874; PMCID: PMC4117366.

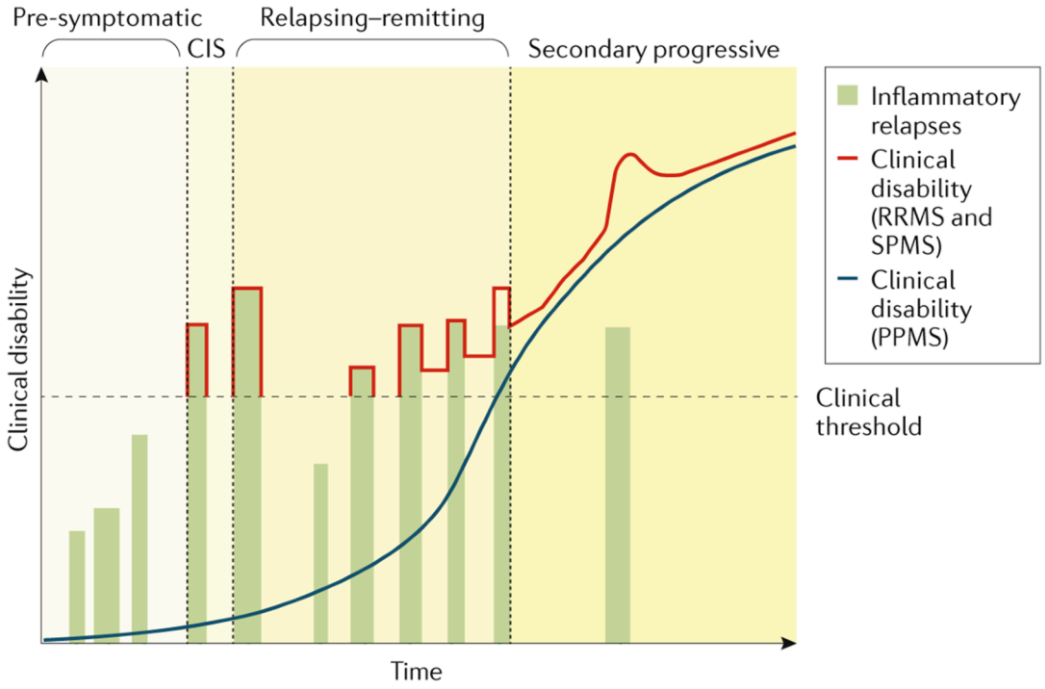
generally retains more inflammatory activity, especially in the earlier years of the progressive phase. SPMS is more prevalent in women, consistent with the higher incidence of RRMS among females.

From a treatment perspective, PPMS has limited therapeutic options, with ocrelizumab being the only FDA-approved disease-modifying therapy specifically indicated for PPMS. SPMS, particularly when still “active” (evidenced by relapses or MRI activity), may respond to several disease-modifying treatments used for RRMS, including interferons and newer immunomodulatory agents. However, once SPMS becomes “non-active,” treatment becomes more limited, and management tends to focus on symptom control and supportive care.

In summary, while both PPMS and SPMS involve progressive neurological decline, PPMS begins as a progressive disease, whereas SPMS represents a later phase of RRMS, transitioning from a relapse-driven course to one of steady worsening. Understanding these distinctions is important for prognosis, treatment decisions, and patient counseling.

SPMS carries a significant disease burden and affects a notable proportion of the MS population, with prevalence estimates ranging from 1 to 58 per 100,000 people globally. In the European Union, prevalence ranges from 3 to 50 per 100,000, while in the US, it is estimated at 27 to 45 per 100,000. Despite its importance as a critical turning point in the MS disease course, SPMS is diagnosed retrospectively, typically after a sustained increase in disability.

Figure 1: Clinical Stages and Manifestations of Multiple Sclerosis



Source: Filippi et al., 2018

Non-Active Secondary Progressive Multiple Sclerosis

The classification of SPMS has evolved to include two subtypes: active SPMS, which continues to show evidence of relapses or MRI lesion activity, and non-active SPMS, in which there are no new clinical relapses or new/enlarging MRI lesions, but the patient experiences slow, steady progression of disability[13].

Non-Active Secondary Progressive Multiple Sclerosis (Non-Active SPMS) is a stage of multiple sclerosis characterized by a gradual and continuous worsening of neurological function without evidence of ongoing inflammatory activity[14]. This form of the disease typically follows an earlier phase known as relapsing-remitting MS (RRMS), in which patients experience clearly defined relapses (flare-ups of new or worsening symptoms) followed by periods of remission. Over time, many individuals with RRMS transition into secondary progressive MS (SPMS), where the primary feature becomes steady neurological decline rather than relapses.

In non-active SPMS, patients no longer experience relapses or show signs of new lesion activity on MRI, such as gadolinium-enhancing lesions or new/enlarging T2 lesions. The disease progresses silently, with increasing physical or cognitive disability over time. Unlike active SPMS, where inflammation still contributes to disease progression, non-active SPMS reflects a more neurodegenerative process that occurs independent of overt immune system attacks[15].

The underlying pathophysiology of non-active SPMS differs from earlier stages. In RRMS and active SPMS, inflammatory processes—mediated by peripheral immune cells such as T and B lymphocytes—drive demyelination and neurodegeneration. In contrast, non-active SPMS is characterized by chronic, compartmentalized inflammation within the CNS and a predominance of neurodegenerative processes. These include mitochondrial dysfunction, axonal loss, microglial activation, and grey matter demyelination. As a result, therapies targeting peripheral inflammation may no longer be effective once the disease has transitioned into this phase.

The underlying pathology of non-active SPMS is believed to involve chronic neurodegeneration, including axonal loss, mitochondrial dysfunction, and damage to both white and gray matter in the brain and spinal cord. These changes accumulate over time, leading to increasing disability in the absence of clinical or radiological markers of inflammation. Because traditional DMTs primarily target the immune response and are most effective in inflammatory phases of MS, they tend to offer limited benefit in non-active SPMS.

Management of non-active SPMS is therefore challenging. With few approved treatments specifically for this phase, care focuses largely on symptom control, rehabilitation, and supportive strategies to maintain independence and quality of life. Most DMTs, including interferons, glatiramer acetate, anti-CD20 monoclonal antibodies (like ocrelizumab), and S1P modulators (like siponimod), are only approved or shown to be beneficial in active SPMS[16]. In non-active SPMS, treatment strategies shift toward symptomatic management. These include pharmacologic interventions for spasticity (e.g., baclofen), fatigue (e.g., amantadine), neuropathic pain (e.g., gabapentin), and bladder/bowel dysfunction. In addition, physical and occupational therapy, mobility support, and mental health care play vital roles in preserving quality of life. However, none of these approaches modify disease progression.

This symptomatic and supportive focus highlights a significant limitation in the current standard of care. The lack of effective treatments that slow or stop neurodegeneration leaves non-active SPMS patients at high risk of continual decline. Another key issue is the difficulty in timely and accurately identifying the transition to SPMS. The diagnosis is typically retrospective and may come years after the transition, by which time anti-inflammatory therapies have limited utility. Moreover, because most clinical trials focus on RRMS or active SPMS populations, non-active SPMS patients are often excluded, reducing the evidence base and innovation directed at this group.

[13] Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS, Thompson AJ, Wolinsky JS, Balcer LJ, Banwell B, Barkhof F, Bebo B Jr, Calabresi PA, Clanet M, Comi G, Fox RJ, Freedman MS, Goodman AD, Inglese M, Kappos L, Kieseier BC, Lincoln JA, Lubetzki C, Miller AE, Montalban X, O'Connor PW, Petkau J, Pozzilli C, Rudick RA, Sormani MP, Stüve O, Waubant E, Polman CH. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology.* 2014 Jul 15;83(3):278-86. doi: 10.1212/WNL.0000000000000560. Epub 2014 May 28. PMID: 24871874; PMCID: PMC4117366.

[14] Ziemssen T, Bhan V, Chataway J, Chitnis T, Campbell Cree BA, Havrdova EK, Kappos L, Labauge P, Miller A, Nakahara J, Oreja-Guevara C, Palace J, Singer B, Trojano M, Patil A, Rauser B, Hach T. Secondary Progressive Multiple Sclerosis: A Review of Clinical Characteristics, Definition, Prognostic Tools, and Disease-Modifying Therapies. *Neurol Neuroimmunol Neuroinflamm*. 2022 Nov 22;10(1):e200064. doi: 10.1212/NXI.0000000000200064. PMID: 36414428; PMCID: PMC9682625.

[15] Ontaneda D, Thompson AJ, Fox RJ, Cohen JA. Progressive multiple sclerosis: prospects for disease therapy, repair, and restoration of function. *Lancet*. 2017 Apr 1;389(10076):1357-1366. doi: 10.1016/S0140-6736(16)31320-4. Epub 2016 Nov 24. PMID: 27889191.

[16] Montalban X, Hauser SL, Kappos L, Arnold DL, Bar-Or A, Comi G, de Seze J, Giovannoni G, Hartung HP, Hemmer B, Lublin F, Rammohan KW, Selmaj K, Traboulsee A, Sauter A, Masterman D, Fontoura P, Belachew S, Garren H, Mairon N, Chin P, Wolinsky JS; ORATORIO Clinical Investigators. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. *N Engl J Med*. 2017 Jan 19;376(3):209-220. doi: 10.1056/NEJMoa1606468. Epub 2016 Dec 21. PMID: 28002688.

Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis, also called Lou Gehrig's disease, is a progressive, fatal neurological disease affecting as many as 16,000 Americans with 5,000 new cases occurring in the United States each year[17]. Related medical care, equipment, and home health care costs can be significant, especially in the later stages of the disease. Symptoms may include loss of equilibrium and/or motor control in hands and arms, difficulty speaking, swallowing and/or breathing, persistent fatigue, and twitching and cramping, which can sometimes be severe. ALS strikes in mid-life and is usually fatal within five years of diagnosis. The causes for ALS are not clearly understood; more work is needed to conclusively determine what factors contribute to its development.[18]

There are two primary types of ALS: sporadic and familial. Sporadic ALS, where there are no other cases known in the patient's family, is the most common form of ALS in the United States, representing 90 to 95% of all cases. Conversely, familial ALS suggests a hereditary basis for the disorder. Only about 5 to 10% of all ALS patients appear to have the genetic or inherited form of ALS. In those families, there is a 50% chance each offspring will inherit gene mutation and may therefore develop the disease[19].

The disorder belongs to a class of maladies known as motor neuron diseases. ALS occurs when specific nerve cells in the brain and spinal cord that control voluntary movement gradually degenerate. The loss of these motor neurons causes the muscles under their control to weaken and atrophy, inevitably leading to paralysis. ALS manifests itself in different ways, depending on which muscles weaken first[20].

Even through the exact pathogenic pathway of ALS is not clear, multiple mechanisms that may be responsible for ALS have been proposed: neuroinflammation, mitochondria dysfunction, glutamate excitotoxicity, oxidative stress, Impaired protein homeostasis, Impaired axonal transport, dysregulated nucleocytoplasmic transport, and cytoskeletal abnormalities, as illustrated in Figure 3[21]. Simply put, ALS reflects disturbances in the microtubule-associated tau protein metabolism. The motor neuron ultimately is significantly disrupted. The microenvironment of the neuron becomes a complex milieu in which high levels of glutamate provide a source of chronic neurotoxicity, and the contribution of activated microglial cells leads to further damage and eventually to motor neuron death.

Neuroinflammation is the best represented therapeutic target covered by a variety of approaches, including modulation of regulatory immune T cells (Tregs). It was discovered in pathological studies that there are immune abnormalities in the CNS, as well as in the blood and cerebrospinal fluid of individuals affected by ALS[22]. Those abnormalities include T cell abnormalities, increased levels of circulating chemokines and cytokines and elevated systemic inflammation. Additionally, the SOD1 animal model of ALS also exhibits signs of inflammation and immune abnormalities suggesting that the immune system may play a role in the development of the disease. The immune and inflammatory changes observed in ALS might be one of the primary contributors to the disease, that further damages the neurons and exacerbates injury. On the other hand, neuroinflammation and T cell infiltration could be a secondary response to the tissue damage that occurs in ALS, similar to other types of nervous system injuries. Once present, inflammation and immune changes could either enhance damage or have a protective effect. The protective aspects of inflammation include the removal of debris by microglia, which is essential for repair, and interaction with T cells. Brain-specific T cells at the site of injury can also contribute to repairing damaged or inflamed tissues, which are known as "protective immunity." This process is probably due to the cytokines and growth factors delivered by T cells to the injury site. Protective immunity appears to be a general and homeostatic phenomenon.

[17] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6735526/
[18] http://www.nih.gov
[19] http://www.als.org
[20] Xiong ZQ *et al*., Neuron 2002 (35): 1011
[21] Mead, R.J., Shan, N., Reiser, H.J. et al. Amyotrophic lateral sclerosis: a neurodegenerative disorder poised for successful therapeutic translation. Nat *Rev Drug Discov* 22, 185–212 (2023). https://doi.org/10.1038/s41573-022-00612-2
[22] McCombe PA, Henderson RD. The Role of immune and inflammatory mechanisms in ALS. *Curr Mol Med.* 2011 Apr;11(3):246-54. doi: 10.2174/156652411795243450. PMID: 21375489; PMCID: PMC3182412

Standard of Care in ALS

Currently, there is no cure for ALS, nor is there a proven therapy that prevents or reverses the course of the disease. The natural history of disease progression demonstrated in the PRO-ACT database, the largest ALS data repository, showed that the average rate of patient decline is 1 point/month on the ALSFRS-R functional rating score (Figure 3, left panel). There are only three FDA-approved drugs for ALS: Rilutek, RADICAVA and RELYVIRO.

Rilutek (riluzole, oral pill) can prolong survival modestly of ALS patients but will not help patients regain muscle strength[23]. Using the Wilcoxon test, the treatment groups gained 90 and 60 days of median survival in two pivotal Phase 3 trials, with 95% confidence intervals. There was no statistically significant difference in mortality at the end of the study[24].

RADICAVA (edaravone). In a registration trial, RADICAVA (edaravone), chronically administered via an intravenous infusion, was shown to improve the ALSFRS-R scale[25] by 2.5 points (scale from 0-48) at 24 weeks[26]. Treated patients declined by 5 points, while placebo patients experienced a 7.5-point decrease (Figure 4, right panel). Ninety percent of patients enrolled in the trial were also taking oral Rilutek. Neither of these drugs alters the course of the disease significantly. The mechanism by which Rilutek and RADICAVA function has not been elucidated.

RELYVRIO. The latest drug to be approved is RELYVRIO (sodium phenylbutyrate and taurursidol combined) provided a 3.3-point benefit on the ALSFRS-R, when compared to placebo at 24 weeks (Figure 4, middle panel).[27] In a post-hoc long-term survival analysis of the RELYVRIO trial indicated that while there is no difference in terms survival between the drug and placebo up to 12 months, there is a separation between the curves between 18 and 32 months, providing a median survival benefit of ~4 months. This information is not included in the prescription information for RELYVRIO.

Amylyx (AMLX; Not Rated) announced in April 2024 that it had initiated the voluntary withdrawal process for RELYVRIO from the market due to its failure to demonstrate efficacy in a significant clinical trial. Relyvrio would not be accessible for new patients. However, for patients currently undergoing treatment in the US and Canada who, in consultation with their healthcare provider, choose to continue therapy can transition to a complimentary drug program. The decision was followed by the findings from a large-scale Phase 3 clinical trial that was disclosed in early March, revealed that RELYVRIO provided a benefit similar to placebo measured by the ALS functional scale (evaluating breathing, swallowing, and speech abilities over a 48-week period). Additionally, it did not notably enhance patient-reported quality of life, overall survival, or respiratory function.

QALSODY. In April 2023, the FDA approved QALSODY (tofersen) as a treatment for individuals suffering from ALS linked to a mutation in the superoxide dismutase 1 (SOD1) gene, known as SOD1-ALS. Mutations in the SOD1 gene are the second-most common cause of familial ALS, found in about 10-20% of familial cases and 1-2% of sporadic cases of ALS. Qalsody, an antisense oligonucleotide, targets SOD1 mRNA to diminish the production of the SOD1 protein. The approval decision was based on measurements of plasma neurofilament light (NFL), which serves as a blood-based indicator for nerve damage and the progression of neurodegeneration. The trial failed to achieve a significant improvement over placebo, when measured by the ALSFRS-R (NCT02623699). However, based on trends observed on multiple secondary endpoints, including NFL, Biogen (BIIB; Not Rated) submitted an NDA to the FDA. Following an advisory panel review, the drug was approved on an accelerated basis in April 2023. We consider tofersen not a directly competing drug against COYA-302 due to its narrow applicability for the overall ALS population.

[23] http://www.mdausa.org
[24] http://aventispharma-us.com/Pls/riluteck_TXT.html
[25] The ALSFRS-R scale consists of 12 questions that evaluate the fine motor, gross motor, bulbar, and respiratory function of patients with ALS (speech, salivation, swallowing, handwriting, cutting food, dressing/hygiene, turning in bed, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency). Each item is scored from 0-4, with higher scores representing greater functional ability
[26] https://www.radicavahcp.com/assets/dist/pdfs/radicava-prescribing-information.pdf
[27] https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/216660s000lbledt.pdf

Figure 2: Glossary of Terms - ALS

ALSFRS: Amyotrophic Lateral Sclerosis Functional Rating Scale. It is a measure of disability in ALS patients

ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised. It includes more functional assessments than ALSFRS

Amyotrophic Lateral Sclerosis (ALS): A chronic, progressive disease marked by gradual degeneration of the nerve cells in the central nervous system that control voluntary muscle movement. The disorder causes muscle weakness and atrophy

Antigen-Presenting Cells (APCs): A group of immune cells that are capable of processing and presenting antigens for recognition by T cells to initiate the adaptive cellular immune responses

Blood–Brain Barrier (BBB): A highly selective semipermeable border of endothelial cells that prevents solutes in the circulating blood from non-selectively crossing into the extracellular fluid of the central nervous system where neurons reside

Cell Adhesion Molecules (CAMs): A subset of cell surface proteins that are involved in the binding of cells with other cells or with the extracellular matrix

Cerebrospinal Fluid (CSF): Clear, colorless body fluid found within the tissue that surrounds the brain and spinal cord

CTLA-4: Also known as CD152, is a protein receptor that functions as an immune checkpoint and downregulates immune responses

Effector T Cells (Teffs): Functional cells for executing immune functions

Excitotoxicity: Overstimulation of neurons that can lead to neuronal death overtime

Forced Vital Capacity (FVC): Lung function tests that measure total amount of air exhaled

FOXP3: A fork head / winged-helix transcription factor localized on the X chromosome (Xp11.23)

Frontotemporal Dementia (FTD): Result of damage to neurons in the frontal and temporal lobes of the brain. Many possible symptoms can result, including unusual behaviors, emotional problems, trouble communicating, difficulty with work, or difficulty with walking

Interleukin-2 (IL-2): An interleukin, a type of cytokine signaling molecule in the immune system

Oxidized Low-Density Lipoprotein (oxLDL): A product of lipid oxidation, is considered as a marker of oxidative stress

Motor Neuron: Nerve cells that conveys impulses initiating muscle contraction or glandular secretion

Natural Killer Cells (NK Cells): A type of immune cell that has granules (small particles) with enzymes that can kill tumor cells or cells infected with a virus

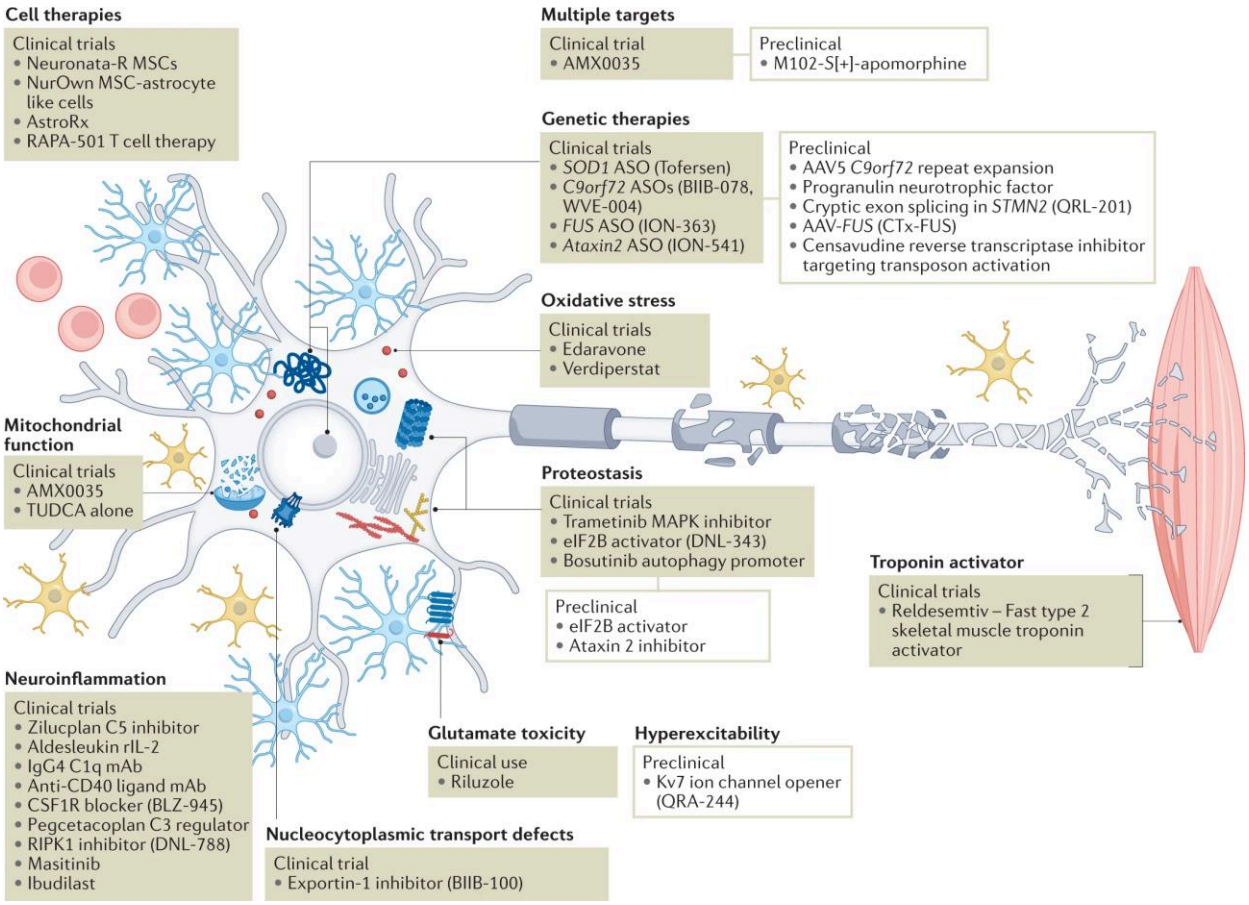
Oxidized Low-Density Lipoprotein (oxLDL): Measures protein damage due to oxidative. modification of the apolipoprotein B (ApoB) subunit on low- density lipoprotein cholesterol (LDL-C)

Primary Progressive Aphasia (PPA): A type of dementia, caused by damage to parts of the brain that control our language, personality, emotions, and behavior

Regulatory Immune T cells (Tregs): A specialized subpopulation of T cells that act to suppress immune response, thereby maintaining homeostasis and self-tolerance

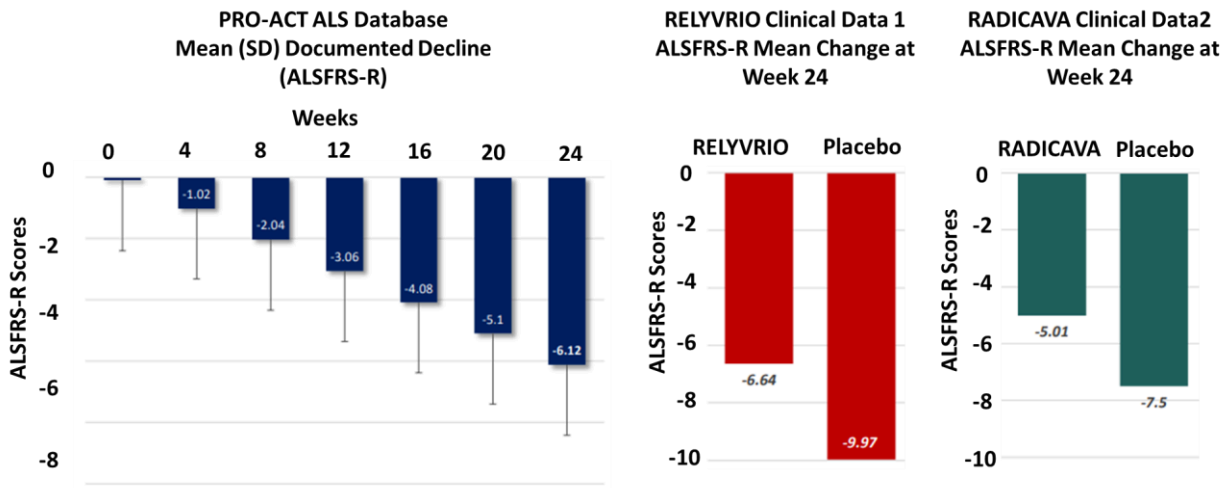
Selective Serotonin Reuptake Inhibitors (SSRIs): The most commonly prescribed antidepressants. They can ease symptoms of moderate to severe depression, are relatively safe and typically cause fewer side effects, by increasing levels of serotonin in the brain through blocking the reabsorption of serotonin into neurons

Figure 3: Biochemical Mechanisms Potentially Involved in ALS



Source: Mead, R.J., Shan, N., & Reiser, H.J. et al. Nat Rev Drug Discov. 2023. 22, 185–212.

Figure 4: Efficacy of Current Standard of Care for ALS



Source: Coya Therapeutics Corporate Presentation, April 2024.

Alzheimer's Disease (AD)

Alzheimer's disease, the most common adult form of dementia, is a devastating neurological disease, estimated to affect 7M Americans[28] and over 416M worldwide[29], with an average course of about 8 to 10 years. Of all individuals over 65 years, an estimated 11% have AD and this rate exceeds 35% at age 85 years and older. About 50% of all AD patients have early or mild diseases, with the remainder having moderate-to-severe AD. The projected prevalence of AD will double over every 20 years[30]. By 2050, over 16M Americans may have AD. In 2023, the cost of caring for AD patients is running at $345B in the US.[31]. Approximately 500,000 new cases of AD will be diagnosed in 2023[32]. Nearly 1 in 5 caregivers of Alzheimer's patients say taking care of their family members or friends has made their health worse. In 2024, Medicare and Medicaid will spend $231B yearly on care for AD sufferers[33], and the average Medicare costs for an AD patient are ~$30,000 a year average, compared to ~$17,000 per year Medicare cost for same-risk beneficiaries without dementia[34].

AD is an age-associated neurodegenerative disorder pathologically characterized by the abnormal accumulation of intracellular neurofibrillary tangles (NFTs) and extracellular amyloid plaques in selected brain regions. The main clinical manifestations of AD include the insidious onset and gradual progression of cognitive impairment affecting multiple domains. Impaired recent memory (difficulty learning new information) is the clinical hallmark of AD; other signs include disturbances in language, visual-spatial processes, and executive control functions such as insight and judgment. Alterations in behavior (e.g., irritability, paranoia), mood (e.g., depression), and personality (e.g., apathy) often cause much agony and frustration for relatives and caregivers of AD patients.

Therapy in AD involves pharmacologic strategies that are either symptomatic or neuroprotective. Although symptomatic and neuroprotective treatments may have similar outcomes in a clinical trial, the latter is expected to have a cumulative benefit persisting after the patient stops treatment. Currently available pharmacologic therapies, including acetylcholinesterase (AChE) inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists, only treat symptoms and do not address the underlying neurodegeneration. Currently, the leading therapeutic agents for AD include Aricept (donepezil), an AChE inhibitor approved in 1996 and Namenda (memantine), an NMDA receptor antagonist which entered the market in 2003. Several other AChE inhibitors are on the market, notably Exelon (rivastigmine), approved in 2000 and Razadyne (galantamine, formerly known as Reminyl), which was approved in 2001. Cognex (tacrine) was the first drug approved for AD treatment, in 1993. The first biologic drug, Aduhelm (aducanumab) was approved in 2021, but withdrawn in 2024 for lack of significant commercial uptake. A follow-on antibody, Leqembi (lecanemab) was approved in 2023. The approval of yet another antibody, with a similar mode of action, donanemab, was recently delayed by the FDA.

AD is the most common form of dementia[35], a disease of the nervous system characterized by loss of certain mental abilities. This loss is severe enough to interfere with normal activities and lasts at least 6 months. AD is not present at birth but usually develops during the aging process. It is marked by a gradual decline in mental functions such as memory, reasoning, and the ability to plan and schedule tasks or events[36]. The first stages include a slight loss in memory, such as the inability to remember the names of people or objects. As the disease develops, a person loses the ability to carry out familiar tasks, to reason, and to exercise judgment. Moods, personality, and ability to communicate may also be affected. People with AD typically die within 8-10 years of their diagnosis. Some individuals may die within a year of diagnosis, while others may live as long as 20 years. AD is the fourth leading cause of death among adults in the US after heart disease, cancer, and stroke. Over 4M Americans have AD and 16M are expected to have the disease by the middle of the 21st century[37] . This growth is primarily due to the aging of the US population as a whole.

One form of AD, called early-onset AD, affects people in their 40's and 50's, but most AD patients are >65 years old. About 3% of those between ages 65 and 74 have the disease compared to 19% of those between ages 75 and 84, and 47% of those over 84 years of age.

[28] Alzheimer's Association. (n.d.). 2022 Alzheimer's disease facts and figures. Retrieved from https://www.alz.org/alzheimers-dementia/facts-figures
[29] Gustavsson A, Norton N, Fast T, Frölich L, Georges J, Holzapfel D, Kirabali T, Krolak-Salmon P, Rossini PM, Ferretti MT, Lanman L, Chadha AS, van der Flier WM. Global estimates on the number of persons across the Alzheimer's disease continuum. *Alzheimer's Dement*. 2023 Feb;19(2):658-670. doi: 10.1002/alz.12694. Epub 2022 Jun 2. PMID: 35652476.
[30] Alzheimer's Disease International. (n.d.). Dementia statistics.
[31] Alzheimer's Association 2023 Facts and Figures report.
[32] Alzheimer's San Diego. (n.d.). Facts & Stats.
[33] Alzheimer's Impact Movement. (n.d.). Alzheimer's Disease Facts and Figures.
[34] Pyenson B, Sawhney TG, Steffens C, Rotter D, Peschin S, Scott J, Jenkins E. The Real-World Medicare Costs of Alzheimer Disease: Considerations for Policy and Care. *J Manag Care Spec Pharm*. 2019 Jul;25(7):800-809. doi: 10.18553/jmcp.2019.25.7.800. PMID: 31232206; PMCID: PMC10398271.
[35] https://www.cdc.gov/aging/aginginfo/alzheimers.htm#:~:text=Alzheimer's%20disease%20is%20the%20most,thought%2C%20memory%2C%20and%20language
[36] Alzheimer's Research Forum (http://www.alzforum.org/)
[37] Hebert *et al*., *Archives of Neurology* 60: 1119 – 1122 (2003)

Figure 5: Alzheimer's Disease Terminology

Acetyl choline – an important neurotransmitter, which is released when neurons communicate and transmit signals to each other

Acetyl cholinesterase – an enzyme that degrades the neurotransmitter acetyl choline, normally found where two nerves communicate

Alzheimer's disease – a debilitating, age-related neurodegenerative disorder most commonly linked to memory loss and cognitive deficit

β–amyloid – an abnormal protein deposited between and within cells. Amyloid stains with Congo Red or Thioflavin S and is linked to Alzheimer's Disease. Amyloid is abnormally deposited in neuritic plaques and in small blood vessels.

Amyloid Precursor Protein (APP) – a protein of uncertain function that is normally found in the brain. In Alzheimer's, APP is abnormally processed and degraded resulting in the formation of amyloid

Apoptosis – also known as programmed cell death; a type of cell death in which the cell uses specialized cellular machinery to kill itself; a cell suicide mechanism also associated with pathology in disease and particularly with neurodegeneration in Alzheimer's disease

Axon – portion of a nerve cell that transmits impulses to a neighboring cell or the destination of the nerve signal; insulated and protected by myelin sheaths (produced by oligodendrocytes in the central nervous system)

Blood-brain barrier (BBB) – a layer of endothelial cells that separates the brain from the bloodstream, with the exception of the fine vessels that supply brain cells with nutrients and the small population of immune cells that conduct routine immunosurveillance of the brain

Cerebrospinal fluid (CSF) – fluid found surrounding the spinal cord (contains lymphocytes, antibodies, and various other substances)

Cerebrovascular – of or involving the brain and its associated blood vessels

Excitotoxicity – a condition wherein neurons are over-stimulated, causing damage and eventual cell death, e.g. when NMDA receptors are activated by glutamate. Excitotoxicity can be mediated by the influx of calcium ions and/or the transcription of pro-apoptotic genes

Glutamate – the most abundant excitatory neurotransmitter in the nervous system, which binds to specific receptors. In excess, glutamate can cause excitotoxicity, which renders neurons vulnerable and can even cause them to die

Immunotherapy – a therapeutic approach to treating Alzheimer's disease that involves activating the body's own immune system against amyloid protein, thus breaking up plaques in the brain and reducing neuronal death

Magnetic Resonance Imaging (MRI) – a method of producing extremely detailed pictures of the living brain using electromagnetic energy released when exposing a patient to radio waves in a strong magnetic field

N-methyl-D-aspartate (NMDA) – an amino acid that is the chief agonist for a particular subset of glutamate receptors in the brain

Neuritic plaques – abnormal networks of proteins surrounding a central core of amyloid; neuritic plaques, along with neurofibrillary tangles, are the hallmarks of Alzheimer's disease

Neurofibrillary tangles – Abnormal bundles of filaments in nerve cells in the brain. These filaments contact on the structural protein tau and represent one of the typical pathological features of Alzheimer's disease.

NSAIDs – Non-steroidal anti-inflammatory drugs

Oligodendrocytes – the myelinating cells of the central nervous system

Presenilins – integral membrane proteins that form key components of the enzymes known as secretases in the brain; mutations in genes encoding these proteins are strong genetic risk factors for Alzheimer's disease

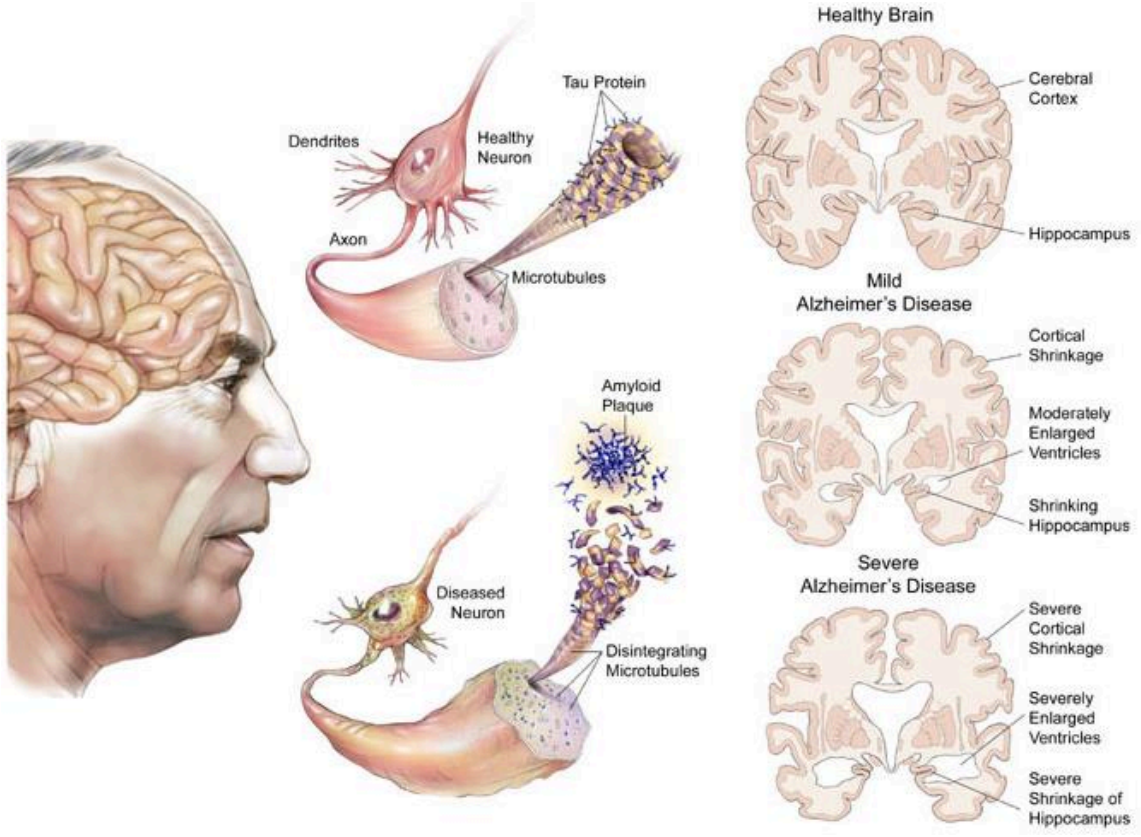
Secretases – enzymes found in brain cells (alpha-secretase, beta-secretase, and gamma-secretase). The secretases degrade APP and their aberrant function can lead to abnormal degradation of APP, causing brain amyloid accumulation and development of Alzheimer's disease

Source: Alzheimer's Disease Research Center (http://www.alzresearch.org/)

AD is characterized clinically by progressive cognitive deterioration together with declining activities of daily living and neuropsychiatric symptoms or behavioral changes. The most striking early symptom is memory loss (amnesia), usually manifests as minor forgetfulness that becomes steadily more pronounced with illness progression, with relative preservation of older memories. As the disorder progresses, cognitive (intellectual) impairment extends to the domains of language (aphasia), skilled movements (apraxia), recognition (agnosia) and those functions (such as decision-making and planning) closely related to the frontal and temporal lobes of the brain as they become disconnected from the limbic system, reflecting extension of the underlying pathological process. This consists principally of neuronal (cell) loss (or atrophy), together with an inflammatory response to the deposition of amyloid plaques and neurofibrillary tangles (NFTs).

Generally, neurologists classify Alzheimer's disease as a disorder marked by significant changes at the tissue level. These changes mirror a loss of cognitive function and usually manifest themselves in the form of characteristic pathological hallmarks of the disease (Figure 6).

Figure 6: Brain Pathology in AD



Source: American Health Assistance Foundation (http://www.ahaf.org/alzdis/about/Brain_Neurons_AD_Normal.htm).

One of the so-called hallmarks of AD is the accumulation of amyloid plaques between nerve cells (neurons) in the brain. The main component of these plaques, or protein clumps, is the protein fragment known as amyloid. This is a fragment of a protein that is snipped from another protein called amyloid precursor protein (APP). In a healthy brain, these protein fragments would be broken down and eliminated. In AD, the fragments accumulate to form hard, insoluble plaques. The second chief pathological hallmark of AD consists of neurofibrillary tangles, which are composed of insoluble twisted fibers that are found inside of the brain's cells. They primarily consist of a protein called tau, which forms part of a structure called a microtubule. The microtubule helps transport nutrients and other important substances from one part of the neuron to another. In Alzheimer's disease the tau protein is abnormal and the microtubule structures collapse. There is an overall shrinkage of brain tissue as Alzheimer's disease progresses. In addition, the ventricles, or chambers within the brain that contain cerebrospinal fluid, are noticeably enlarged. In the early stages of Alzheimer's disease, short-term memory begins to decline when the cells in the hippocampus, which is part of the limbic system, degenerate.

There are three major competing hypotheses to explain the cause of the disease.

The oldest hypothesis is the "*cholinergic hypothesis*", which states that AD begins as a deficiency in the production of acetylcholine, a vital neurotransmitter. Much early therapeutic research was based on this hypothesis, including restoration of the "cholinergic nuclei". The possibility of cell-replacement therapy was investigated based on this hypothesis. All the first-generation anti-Alzheimer's medications are based on this hypothesis and work to preserve acetylcholine by inhibiting acetyl cholinesterase (enzymes that break down acetylcholine). These medications, though sometimes beneficial, have not led to a cure. In all cases, they have served to only treat symptoms of the disease and have neither halted nor reversed it. These results and other research have led to the conclusion that acetylcholine deficiencies may not be directly causal, but are a result of widespread brain tissue damage, damage so widespread that cell-replacement therapies are likely to be impractical.

The other two hypotheses each have their advocates and have often been described (lightheartedly) as the "tau-ist" and "ba-ptist" viewpoints in scientific publications by Alzheimer's disease researchers. "Tau-ists" believe that the tau protein abnormalities come first and lead to a full disease cascade. "bA-ptists" believe that β-amyloid deposits are the causative factor in the disease. For example, the presence of the APP gene on chromosome 21 is believed to explain the high incidence of early-onset AD pathology in patients with Down syndrome, who carry three copies of chromosome 21 and thus APP itself. The "ba-ptist" theory is finding new supporters due to recent discoveries of impaired vascular and cerebrospinal fluid transport of β-amyloid out of the brain tissues, resulting in a greater risk for plaque formation. A third protein, alpha-synuclein (α-synuclein), which has already been shown to be important in Parkinson's disease, has also been demonstrated to be associated with amyloid plaques in AD. This hypothesis has been given the name "syn-ners" among AD researchers. There is also a "triple lesion" hypothesis that proposes a pathological interaction among these three candidate proteins. The extent of each protein's contribution may determine whether the "lesion disorder" manifests as AD, Parkinsonism, or other degenerative diseases.

Comparison of Assessment Instruments

While not exhaustive, this list includes all the tests used very frequently and includes a variety of different types of tests so that the strengths and weaknesses of various approaches can be discussed.

The Mini Mental State Exam (MMSE): An 11-item test with a total score of 0 (severe impairment) to 30 (no impairment)[38]. It is probably the most widely used screening instrument for dementia in the world and has been widely used in clinical trials. It includes very brief assessments of memory, language, praxis, and orientation. Major strengths of the MMSE include its coverage of a variety of relevant cognitive areas in a very brief test and the availability of large amounts of cross-sectional and longitudinal data. One weakness is that it is likely too brief, particularly in its assessment of memory, to be very sensitive, and non-specific carry-over effects make it difficult to use in trials where patients are assessed many times.

Alzheimer's Disease Assessment Scale—cognitive sub-scale (ADAS-cog)[39]: probably the most widely used cognitive assessment instrument in clinical trials of anti-dementia drugs done in the US and has been recognized by the FDA. Although less well known outside the United States, this scale has been used extensively in Europe, where it has been recognized as acceptable by the Commission of the European Communities, and in Japan. The cognitive portion includes 7 performance items and 4 clinician-rated items assessing memory, language, praxis, and orientation, with a total score ranging from 0 (no impairment) to 70 (severe impairment). The non-cognitive portion includes 10 clinician-rated items assessing psychosis, agitation, depression, and other abnormalities. Strengths of the scale are its broad coverage of relevant cognitive domains, its widespread use, the availability of alternate forms for the memory tests, and the availability of extensive longitudinal data.

[38] Hooten and Lyketsos. *Dementia and Geriatric Cognitive Disorders* 9: 164-74 (1998)
[39] Gauthier and Ferris. *International Journal of Clinical Practice Supplement* 120: 29-39 (2001)

Weaknesses are that it is somewhat long (approximately 45 minutes per administration) and that severely demented patients cannot be assessed with this instrument.

Neuropsychological Battery of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD)[40]. The CERAD project was funded by the US National Institute on Aging (NIA) with the aim of developing standardized methods for the clinical, neuro-psychological, neuropathological, and neuro-radiological evaluation of patients with AD. The CERAD neuropsychological battery consists of seven subtests including the MMSE and three others that are adapted from the ADAS-cog rating instrument. These tests assess memory, language, praxis, and orientation. Because the tests were designed to characterize patients along different dimensions, there is no established algorithm for calculating a single dementia severity score. Advantages of the CERAD battery are its broad coverage of cognitive domains, applicability to a broad range of dementia severity, the availability of extensive longitudinal data, and the utility of the battery for measuring symptoms in early AD. The disadvantages are that alternate forms are not readily available, the lack of an obvious summary measure, and its extensive overlap with other instruments.

Clinician's Interview Based Impression of Change that requires the use of caregiver information (CIBIC-plus)[41]: while this is not a single instrument and is not standardized, like the ADAS-cog, clinical trials for investigational drugs have often used a variety of CIBIC formats, each different in terms of depth and structure. As such, results from a CIBIC-plus reflect clinical experience from the trial or trials in which it was used and cannot be compared directly with the results of CIBIC-plus evaluations from other clinical trials. The CIBIC-plus typically examines 4 major areas of patient function: General, Cognitive, Behavioral and Activities of Daily Living. It represents the assessment of a skilled clinician based upon his/her observations at an interview with the patient, in combination with information supplied by a caregiver familiar with the behavior of the patient over the interval rated. The CIBIC-plus is scored as a 7-point categorical rating, ranging from a score of 1, indicating "markedly improved", to a score of 4, indicating "no change" to a score of 7, indicating "markedly worse". CIBIC-plus has not been systematically compared directly to assessments not using information from caregivers or other global methods.

Neuropsychiatric Inventory (NPI)[42]: this instrument was developed to assess psychopathology in dementia patients. It evaluates a set of neuropsychiatric disturbances common in dementia, including delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, loss of inhibition, aberrant motor behavior, and nighttime behavior disturbances. The severity and frequency of each neuropsychiatric symptom are rated based on scripted questions administered to the patient's caregiver. The NPI also assesses the amount of caregiver distress engendered by each of the neuropsychiatric disorders. A total NPI score, and a total caregiver distress score are calculated, in addition to the scores for the individual symptom domains. Content validity, concurrent validity, inter-rater reliability, and test-retest reliability of the NPI are established. Different neurologic disorders have characteristic neuropsychiatric manifestations and distinctive NPI profiles. The NPI is sensitive to treatment effects and has demonstrated the amelioration of behavioral symptoms in Alzheimer's disease by cholinergic agents. The NPI is a useful instrument for characterizing the psychopathology of dementia syndromes, investigating the neurobiology of brain disorders with neuropsychiatric manifestations, distinguishing among different dementia syndromes, and assessing the efficacy of treatment.

All these tests have been shown to measure deterioration in AD patients followed over time and to be relatively insensitive to age-related cognitive changes in non-demented elderly persons.

With all these instruments, the reliability of measured change increases with longer follow-up. This has implications for the design of clinical trials, particularly those in which the aim is not to determine the acute effects of a drug, but to determine the ability of the drug to alter the course of the illness[43]. Regardless of other parameters, the sample size needed for such studies is over twice as large when drug and placebo patients are compared for 6 months than when they are compared for 12 months. This is because the mean changes relative to standard deviation of change increases dramatically as patients are followed for longer periods.

[40] Chandler *et al*., *Neurology* 65: 102-6 (2005)
[41] Schneider LS, Olin JT. Clinical global impressions in Alzheimer's clinical trials. *Int Psychogeriatr*. 1996 Summer;8(2):277-88; discussion 288-90. doi: 10.1017/s1041610296002645. PMID: 8994897.
[42] Cummings *et al*., *Neurology* 44: 2308-14 (1994)
[43] Caban-Holt *et al*., *Geriatrics Supplement*: 3-8 (2005)

Immunotherapy for Alzheimer's Disease

Aducanumab (commercially known as Aduhelm) is a recombinant, human immunoglobulin G1 monoclonal antibody designed to target amyloid β (Aβ) aggregates[44]. In June 2021, it became the first drug to address the underlying pathology of AD to receive approval from the FDA. The FDA's decision was based on aducanumab's ability to clear Aβ plaques, although there was no conclusive evidence linking Aβ clearance to reduced cognitive or functional decline. This decision sparked significant debate within the scientific community, particularly due to the disparate results from the EMERGE and ENGAGE Phase 3 trials. Even after *post hoc* analysis, the data were deemed insufficient to establish aducanumab's efficacy. Moreover, concerns have been raised regarding the approval's potential hindrance to progress, as well as regarding aducanumab's cost and safety profile. The rejection of aducanumab by the EMA in December 2021 further intensified the controversy surrounding the FDA's decision. The EMA determined that findings from clinical trials were inconsistent and did not demonstrate conclusively that the medication effectively treated individuals with early-stage Alzheimer's disease.

Donanemab is a humanized antibody currently under investigation as a treatment for AD[45]. It targets the N-truncated pyroglutamate amyloid-β peptide at position 3 (pGlu3-Aβ, AβpE3). pGlu3-Aβ peptides play a significant role in fostering the accumulation of Aβ peptides, which ultimately results in neurodegeneration and memory decline in Alzheimer's disease. The modification of Aβ with pyroglutamate (pGlu) has been shown to be facilitated by the enzyme glutaminyl cyclase (QC), thereby intensifying its pathogenic and neurotoxic effects. Strategies to address pGlu3-Aβ include reducing its formation by inhibiting the QC responsible for generating N-truncated Aβ to pGlu-Aβ. Donanemab aims to clear pGlu-Aβ post-formation and/or prevent aggregation. Donanemab demonstrates strong affinity for amyloid plaques, particularly cored plaques in the CNS.

In May 2023, Eli Lilly (LLY; Not Rated) announced favorable outcomes from the TRAILBLAZER-ALZ 2 Phase 3 trial[46], indicating that donanemab significantly decelerated cognitive and functional deterioration in individuals with early symptomatic Alzheimer's disease. Donanemab successfully met the primary endpoint, which assessed changes in the integrated Alzheimer's Disease Rating Scale (iADRS) from baseline up to 18 months. Additionally, all secondary endpoints relating to cognitive and functional decline were achieved, demonstrating significant clinical advantages with similar degrees of effectiveness.

TRAILBLAZER-ALZ 2 Phase 3 trial enrolled 1,736 individuals with early symptomatic Alzheimer's disease and evidence of amyloid and tau pathology. Those individuals were categorized based on their level of the brain protein tau, which serves as a prognostic marker for the progression of Alzheimer's disease. Donanemab consistently led to a significant decrease in brain amyloid plaque levels among participants across all evaluated time intervals, with 80% (in the low/medium tau subgroup) and 76% (in the overall participant population) achieving clearance of amyloid plaques by the end of 18 months. The primary analysis group, consisting of 1,182 individuals, was selected for adequate statistical power, and comprised individuals with an intermediate tau level and clinical symptoms indicative of Alzheimer's disease. Within this group, the primary endpoint iADRS revealed a 35% reduction in decline ($p<0.0001$), while a significant secondary endpoint (Clinical Dementia Rating-Sum of Boxes, or CDR-SB) demonstrated a 36% decrease in decline ($p<0.0001$) over the 18-month period.

The anticipated FDA action on donanemab, initially expected in the first quarter of 2024, was postponed to June 10, 2024. While it is uncommon for an advisory committee to occur after the expected FDA action date, this meeting for donanemab follows a similar pattern to meetings for two other FDA-approved therapies targeting amyloid plaque. A group of independent experts advising the FDA supported the utilization of donanemab and concluded that the advantages of the drug surpass the documented risks, which may entail brain swelling and bleeding. On July 2, 2024, the FDA approved donanemab (Kisunla™) for the treatment of individuals with early symptomatic AD. This includes those with mild cognitive impairment and the mild dementia stage of the disease, confirmed by the presence of amyloid plaques. Kisunla, administered once a month, is the first and only therapy targeting amyloid plaques that has shown evidence supporting the discontinuation of treatment once amyloid plaques are eliminated. This approach can lead to reduced treatment costs and fewer infusions.

Lecanemab, sold under the brand name Leqembi, is a monoclonal antibody medication used for the treatment of AD. In January 2023, the FDA granted approval for Leqembi using the Accelerated Approval pathway for AD treatment. Leqembi is the second medication in a novel category approved for Alzheimer's disease, aimed at addressing the core disease

[44] Coerver K, Yu MM, D'Abreu A, Wasserman M, Nair KV. Practical Considerations in the Administration of Aducanumab for the Neurologist. *Neurol Clin Pract*. 2022 Apr;12(2):169-175. doi: 10.1212/CPJ.0000000000001144. PMID: 35733944; PMCID: PMC9208401.
[45] Rashad A, Rasool A, Shaheryar M, Sarfraz A, Sarfraz Z, Robles-Velasco K, Cherrez-Ojeda I. Donanemab for Alzheimer's Disease: A Systematic Review of Clinical Trials. *Healthcare (Basel)*. 2022 Dec 22;11(1):32. doi: 10.3390/healthcare11010032. PMID: 36611492; PMCID: PMC9818878.
[46] Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, Wessels AM, Shcherbinin S, Wang H, Monkul Nery ES, Collins EC, Solomon P, Salloway S, Apostolova LG, Hansson O, Ritchie C, Brooks DA, Mintun M, Skovronsky DM; TRAILBLAZER-ALZ 2 Investigators. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. *JAMA*. 2023 Aug 8;330(6):512-527. doi: 10.1001/jama.2023.13239. PMID: 37459141; PMCID: PMC10352931.

mechanism of amyloid accumulation. The accelerated approval relied on Phase 2 findings, which showed that Leqembi decreased the buildup of Aβ plaque in the brain of AD patients. As part of the post-marketing obligation associated with the accelerated approval, the FDA mandated the applicant to conduct a clinical trial, commonly known as a confirmatory study, to validate the expected clinical advantages of Leqembi.

In June 2023, FDA granted full approval to Leqembi for the treatment of AD in adult patients. This decision came after a confirmatory trial confirmed clinical benefits, suggesting that lecanemab has been shown to reduce markers of amyloid in early Alzheimer's disease and reduce decline on clinical endpoints of cognition and function at 18 months. Leqembi marks the first amyloid beta-directed antibody to transition from accelerated approval to traditional approval for Alzheimer's treatment.

In February 2024, Biogen (BIIB; Not Rated) announced that it has stopped developing and marketing Aduhelm, re-prioritizing resources allocated to aducanumab to advance lecanemab and to develop new treatments. The company suggested that patients currently using Aduhelm in the US may have access to Leqembi, which works similarly to Aduhelm, but clinical trials have demonstrated its superior efficacy in decelerating cognitive deterioration in individuals with AD.

Controversy About Aducanumab

Lack of functional efficacy. The controversy began in 2016 when Biogen released findings from the phase 1b PRIME trial of Aducanumab, showing a decrease in amyloid buildup in the brain, with a marginally positive impact on cognition[47]. Subsequent Phase 3 trials, EMERGE and ENGAGE, were conducted with aducanumab. The outcomes of the study indicated that there were no discernible distinctions between the drug and placebo groups concerning primary and secondary clinical outcomes in the conclusive dataset of the ENGAGE trial. Additionally, disparities were noted between the ENGAGE and EMERGE trials. While ENGAGE did not demonstrate a favorable effect compared to the placebo, EMERGE showed amyloid reduction, supported by an ad hoc analysis. The trial outcomes indicated dose-dependent and time-dependent reductions in amyloid. Despite the controversies surrounding the clinical trials, the FDA granted approval for aducanumab.

Safety Concerns. In both EMERGE and ENGAGE trials, adverse events were observed[48]. Specifically, amyloid-related imaging abnormalities (ARIAs) were observed in 34% of participants in the EMERGE trial and 35.5% in the ENGAGE trial. Patients experiencing ARIAs also exhibited additional symptoms, including headache, confusion, dizziness, and nausea.

Patient Eligibility. The mandatory requirement for excluding aducanumab treatment is the presence of abnormal amyloid in the brain. Based on the existing data, about 20–40% of early AD patients do not exhibit abnormal amyloid. Therefore, aducanumab therapy is ineffective for these individuals[49].

Expense. Aducanumab is administered through monthly infusions, which are estimated to cost approximately $56,000 annually[50]. Notably, due to low sales, the expenses have been reduced to $28,000 per year as of December 2021. However, this price remains prohibitively high for most individuals, especially with limited coverage by payors, as discussed below.

Complexity in Payor Coverage. Medicare will provide coverage for Aducanumab solely to beneficiaries participating in a clinical trial sanctioned by CMS or endorsed by the National Institutes of Health (NIH)[51]. The cost has been established at $28,200 annually, excluding expenses related to eligibility assessment, monitoring, side effect management, and drug administration. Only 41% of Medicaid fee-for-service plans have released a coverage policy for aducanumab that is publicly accessible, and there is considerable diversity in these coverage criteria[52]. While most of the commercial plans have established an aducanumab coverage policy, only five plans included aducanumab in their coverage for members. The available coverage policies exhibited minimal consistency regarding the criteria used to assess an adequate treatment response.

Issues Remaining for Lecanemab and Donanemab

[47] Wojtunik-Kulesza K, Rudkowska M, Orzeł-Sajdłowska A. Aducanumab-Hope or Disappointment for Alzheimer's Disease. *Int J Mol Sci.* 2023 Feb 22;24(5):4367. doi: 10.3390/ijms24054367. PMID: 36901797; PMCID: PMC10002282.
[48] Wojtunik-Kulesza K, Rudkowska M, Orzeł-Sajdłowska A. Aducanumab-Hope or Disappointment for Alzheimer's Disease. *Int J Mol Sci.* 2023 Feb 22;24(5):4367. doi: 10.3390/ijms24054367. PMID: 36901797; PMCID: PMC10002282.
[49] Rabinovici GD, Gatsonis C, Apgar C, Chaudhary K, Gareen I, Hanna L, Hendrix J, Hillner BE, Olson C, Lesman-Segev OH, Romanoff J, Siegel BA, Whitmer RA, Carrillo MC. Association of Amyloid Positron Emission Tomography With Subsequent Change in Clinical Management Among Medicare Beneficiaries With Mild Cognitive Impairment or Dementia. *JAMA.* 2019 Apr 2;321(13):1286-1294. doi: 10.1001/jama.2019.2000. PMID: 30938796; PMCID: PMC6450276.
[50] Wojtunik-Kulesza K, Rudkowska M, Orzeł-Sajdłowska A. Aducanumab-Hope or Disappointment for Alzheimer's Disease. *Int J Mol Sci.* 2023 Feb 22;24(5):4367. doi: 10.3390/ijms24054367. PMID: 36901797; PMCID: PMC10002282.
[51] The Commonwealth Fund. (2022, January 4). Medicare's Decision to Cover Alzheimer's Drug Aduhelm: What Will It Mean for Patients and the Program? Retrieved from https://www.commonwealthfund.org/blog/2022/medicares-decision-cover-alzheimers-drug-aduhelm-what-will-it-mean-patients-and-program.
[52] Lin PJ, Levine A, Rucker J, Chambers JD. Variation in Medicaid and commercial payer coverage of aducanumab for Alzheimer's disease. *Alzheimers Dement*. 2023 Aug;19(8):3654-3669. doi: 10.1002/alz.12965. Epub 2023 Feb 28. PMID: 36852834.

Aduhelm's approval was based on the surrogate measure of Aβ clearance, lacking significant demonstration of clinical effects in its clinical trials. In contrast, lecanemab's (Leqembi) and donanemab's (Kisunla) approval relied on favorable clinical trial outcomes, showing a noticeable improvement in cognitive decline. The positive impact of lecanemab and donanemab are likely associated with its primarily binding affinity towards Aβ protofibrils and amyloid-beta plaques, whereas aducanumab and other monoclonal antibodies tend to favor highly aggregated forms of Aβ[53].

The full approval granted by FDA made the Centers for Medicare & Medicaid Services (CMS) cover lecanemab and donanemab broadly. However, neither Leqembi nor Kisunla reverse cognitive damage or halt the progression of the disease, and despite of slowing cognitive decline by five months over an 18-month period for individuals with mild symptoms, some experts have expressed uncertainty about whether the observed delay in memory and cognition decline would be perceptible or meaningful to patients and their families[54]. Additionally, although most cases of brain swelling and bleeding have been mild or moderate and resolved, there have been instances of serious cases. Certain individuals carry a genetic risk factor, specifically the homozygous apolipoprotein E ε4 gene, which may elevate their risk for developing ARIA when taking donanemab. For lecanemab, the agency also issued a black-box warning, the most severe level, cautioning about serious and life-threatening events associated with the drug, including brain bleeding.

Figure 7: Approved Pharmaceutical Drugs for Alzheimer's Disease

Brand Name	Drug	Category	Modality	Mechanism of Action	Year of Approval	Year Loss of Exclusivity
Cognex	Tacrine	Generic (Withdrawal in 2013)	Small Molecule	Acetylcholinesterase (AChE) Inhibitors	1993	2009
Aricept	Donepezil	Generic	Small Molecule	Acetylcholinesterase (AChE) Inhibitors	1996	2012
Exelon	Rivastigmine	Generic	Small Molecule	Acetylcholinesterase (AChE) Inhibitors	1997	2012
Razadyne	Galantamine	Generic	Small Molecule	Acetylcholinesterase (AChE) Inhibitors	2001	2012
Namenda	Memantine	Generic	Small Molecule	N-methyl-D-aspartate (NMDAR) Antagonist	2003	2014
Risperdal	Risperidone	Generic	Small Molecule	Serotonin & Norepinephrine Reuptake Inhibitor	2007 (EU)	2020
Aduhelm	Aducanumab	Branded (Withdrawal in 2024)	Monoclonal Antibody	Aβ Fibrils and Soluble Oligomers	2021	2033
Leqembi	Lecanemab	Branded	Monoclonal Antibody	Soluble Aggregated Aβ, Oligomers / Protofibrils, Insoluble Fibrils	2023	2035
Kisunla	Donanemab	Branded	Monoclonal Antibody	Amyloid-beta (Aβ) plaques	2024	2029

Source: Global Data & Lucid Capital Markets Research

[53] Söderberg L, Johannesson M, Nygren P, Laudon H, Eriksson F, Osswald G, Möller C, Lannfelt L. Lecanemab, Aducanumab, and Gantenerumab - Binding Profiles to Different Forms of Amyloid-Beta Might Explain Efficacy and Side Effects in Clinical Trials for Alzheimer's Disease. *Neurotherapeutics.* 2023 Jan;20(1):195-206. doi: 10.1007/s13311-022-01308-6. Epub 2022 Oct 17. PMID: 36253511; PMCID: PMC10119362.
[54] Expert reaction to FDA accelerated approval of lecanemab for Alzheimer's disease Website: Science Media Centre URL:

Role of Treg Cells in CNS Immunity

Peripheral immunocytes including T cells, B cells, natural killer cells (NK cells), and dendritic cells (DC), are found in different parts of the brain, which can be either neuroprotective or neurotoxic depending on the local environment. $CD4^+$ and $CD8^+$ T cells search for antigens in the cerebrospinal fluid and induce local immune responses when they recognize them. Antigen-presenting cells, macrophages, and dendritic cells in the meninges and choroid plexus work together to affect T cell activity in the brain. T cells can interact with innate cells like microglia and astrocytes, which also impact brain health. When T cells do not recognize antigens, they exit the brain and return to the peripheral circulation through the lymphatic system[55].

In a healthy brain, the entry and exit of immune cells are tightly regulated to maintain proper brain function. However, during inflammation, interactions between immune cells and brain antigens in secondary lymph nodes can cause leakiness in the blood-brain barrier and lead to excessive immune cell migration into the brain, causing inflammation and damage. Even without crossing the blood-brain barrier, T cells can affect brain function through immune signaling and secreted molecules. Therefore, the coordinated immune response, both inside and outside the CNS, could impact neuronal health.

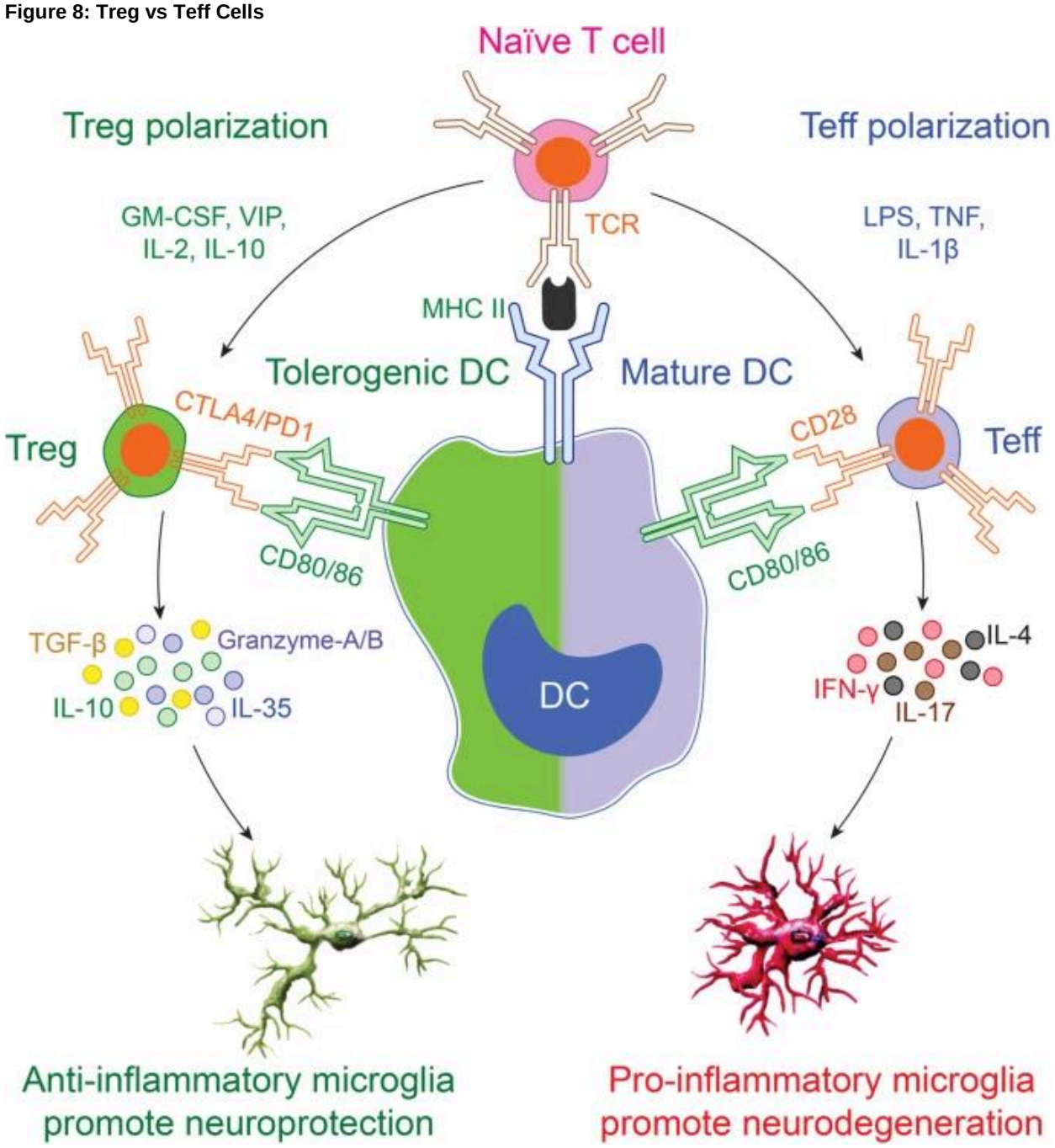
Microglia plays essential roles in maintaining the health of neurons and promoting T cell response in the CNS. Similar to macrophages, which are immune cells found in the rest of the body, microglia can change their behavior and appearance depending on the surrounding environment. They can become pro-inflammatory (M1) or anti-inflammatory (M2) and secrete different molecules that can either damage or protect neurons. Astrocytes, another type of immune cell in CNS, also have different functions and can change their behavior in response to different conditions. In neuroinflammatory and ischemic conditions, astrocytes can have either a harmful (A1) or protective (A2) effect.

The functioning of microglia is regulated by the balance between effector T cells (Teffs) and regulatory T cells (Tregs) cells. Both Teffs and Treg cells originated from T cells, which undergo development in the thymus and differentiated into naïve T cells including $CD8^+$ and $CD4^+$ cells. $CD4^+$ cells can be activated by dendritic cells (DCs) through MHCII-T cell receptor (TCR), which leads to differentiation of effector T cells (Teffs) including Th1 and Th17 cells, and release of pro-inflammatory molecules like IL-10, IL-35, TGF-β, and granzymes.

However, some DCs can maintain immune tolerance by being tolerogenic. These DCs have low levels of co-stimulatory molecules and do not provide enough signals to naïve T cells to activate Teffs or produce pro-inflammatory cytokines like IL-4, IL17, and IFN-γ. Instead, they induce the production of anti-inflammatory cytokines and regulatory T cells (Tregs), which suppress the function and proliferation of Teffs and promote immune tolerance. The balance between Teffs and Tregs is important for maintaining a healthy immune system, as an imbalance can lead to neurodegeneration through microglia responses. Tregs support the polarization of microglia towards an anti-inflammatory state, which is important for neuroprotection (Figure 8).

[55] Machhi J, Kevadiya BD, Muhammad IK, Herskovitz J, Olson KE, Mosley RL, Gendelman HE. Harnessing regulatory T cell neuroprotective activities for treatment of neurodegenerative disorders. *Mol Neurodegener.* 2020 Jun 5;15(1):32. doi: 10.1186/s13024-020-00375-7. PMID: 32503641; PMCID: PMC7275301

Figure 8: Treg vs Teff Cells



Source: Machhi et al., Mol Neurodegener. 2020 Jun 5;15(1):32

Imbalance Between Teff and Treg Cells in Neurodegenerative Diseases

In neurodegenerative diseases, antigens found in the CNS, such as Aβ, α-syn, mSOD, and MBP, trigger immune responses in microglia, leading to an inflammatory cascade in affected areas of the brain[56]. This process involves several steps (Figure 9).

1. First, damaged neurons generate self-antigens or misfolded proteins, which drain to the peripheral lymphoid nodes through meningeal lymphatic vessels. Local antigen-presenting cells (APCs), including macrophages and DCs, take up the natural self-antigens and present them to peripheral T cells in an MHCII-dependent manner.

2. When naive T cells recognize the cognate antigen, they differentiate into antigen-specific Teffs. Reactive microglia then secrete a cytokine-chemokine milieu to upregulate cell adhesion molecules by blood-brain barrier (BBB) endothelial cells, opening the gate for peripheral primed T cells. Teffs with upregulated integrins and cell adhesion molecule (CAM) ligands then cross the BBB and blood-CSF barrier through the choroid plexus meninges. Once Teffs extravasate into the brain, they are reactivated upon recognition of the cognate antigen on common CNS APCs, such as choroid plexus and meningeal macrophages, DCs, and parenchymal microglia.

3. The activated Teffs secrete pro-inflammatory and neurotoxic mediators, polarizing microglia to a higher activation state.

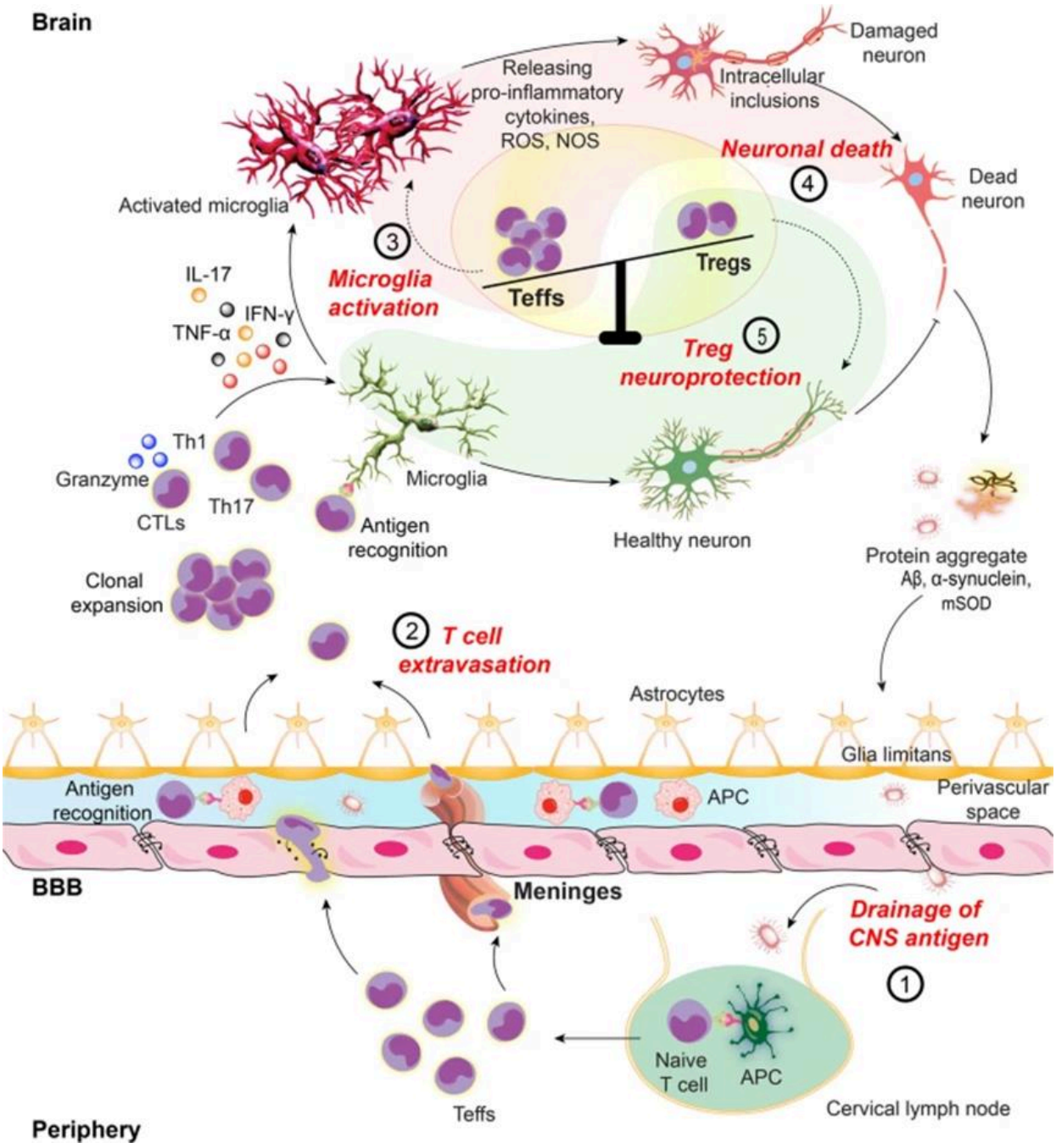
4. Pro-inflammatory cytokines and reactive oxygen and nitrogen species produced by activated microglia further perpetuate the inflammatory cascade and induce neurotoxicity.

5. Finally, Tregs maintain immune tolerance by suppressing effector immune responses. Naïve T cells can differentiate into Tregs when recognizing the cognate antigen on peripheral APCs in secondary lymphoid tissues. Differentiated Tregs exert neuroprotective responses.

The inflammatory immune responses observed in neurodegenerative disorders are the outcome of Teff-Treg imbalances, with upregulated Teff responses.

[56] Machhi J, Kevadiya BD, Muhammad IK, Herskovitz J, Olson KE, Mosley RL, Gendelman HE. Harnessing regulatory T cell neuroprotective activities for treatment of neurodegenerative disorders. *Mol Neurodegener*. 2020 Jun 5;15(1):32. doi: 10.1186/s13024-020-00375-7. PMID: 32503641; PMCID: PMC7275301

Figure 9: Role of Teffs and Tregs in Pathogenetic Pathways in Neurodegenerative Diseases



Source: Machhi et al., Mol Neurodegener. 2020 Jun 5;15(1):32

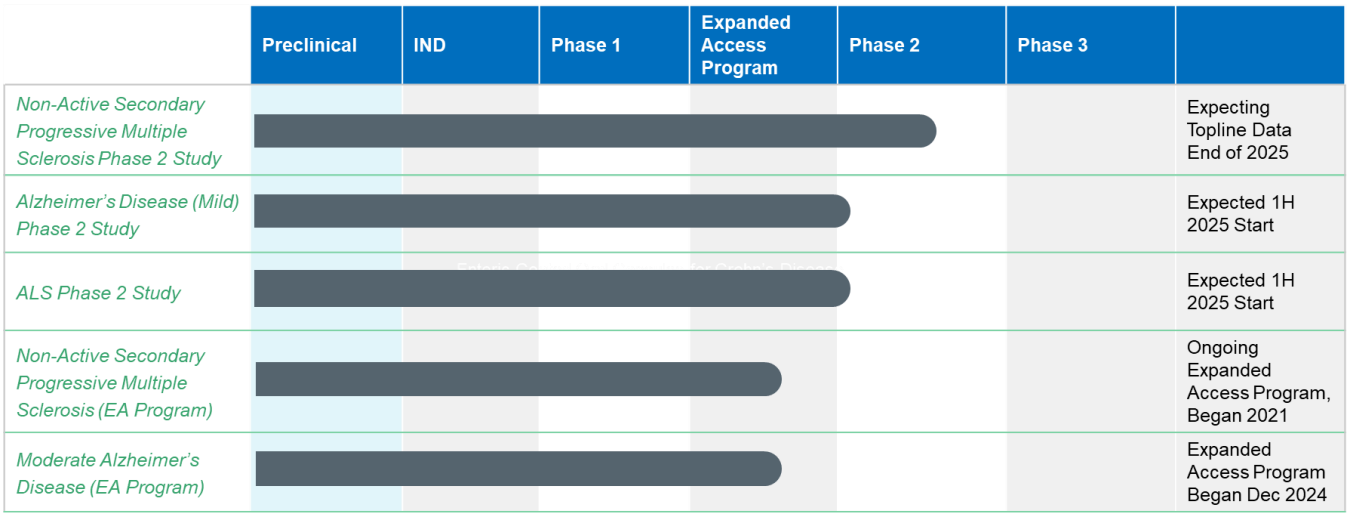
INTRANASAL FORALUMAB: INTRANASAL ANTI-CD3 MONOCLONAL ANTIBODY

Foralumab Overview

Intranasal foralumab is an investigational formulation of foralumab, a fully human anti-CD3 monoclonal antibody, delivered via the intranasal route. It is being developed as a non-invasive immunomodulatory therapy for a range of conditions involving immune dysregulation, including MS, AD and ALS. Unlike traditional anti-CD3 therapies administered intravenously, intranasal delivery of foralumab is designed to modulate the immune system without inducing systemic immune suppression or cytokine release syndrome. The intranasal route targets the mucosal immune system, especially the nasal-associated lymphoid tissue (NALT), aiming to induce regulatory T cell (Treg) responses and dampen pro-inflammatory pathways. This method has shown promise in preclinical and early clinical studies for shifting immune balance toward tolerance rather than systemic activation.

In multiple sclerosis, intranasal foralumab is being studied for its potential to reduce neuroinflammation and slow disease progression by acting on T cells and microglial activation. In other studies, including those for non-active secondary progressive MS (SPMS), it has been associated with reductions in inflammatory markers and improvements in clinical and imaging outcomes. foralumab is being developed by Tiziana Life Sciences, and it represents a novel class of nasal anti-CD3 immunotherapies that aim to provide safe, targeted immune modulation for chronic inflammatory conditions. Ongoing clinical trials are evaluating its safety, efficacy, and long-term benefits.

Figure 10: Intranasal Foralumab Pipeline



Source: Tiziana Life Science Corporate Presentation, June 2025

CD3 Function in T Cell Activation and Autoimmune Regulation

CD3 Overview

CD3 is a core component of the T cell receptor (TCR) complex, playing a critical role in T cell activation and immune regulation[57]. Structurally, CD3 is composed of four subunits—CD3γ, CD3δ, CD3ε, and CD3ζ—which are non-covalently associated with the TCR on all mature T cells (Figure 11). While the TCR is responsible for recognizing antigens presented by major histocompatibility complex (MHC) molecules on antigen-presenting cells, the CD3 complex is responsible for transmitting activation signals into the T cell.

T cell activation begins when the TCR, specifically the αβ heterodimer, recognizes a peptide–MHC (pMHC) complex presented by an antigen-presenting cell at the immunological synapse (Figure 11). Signal transduction is initiated through immunoreceptor tyrosine-based activation motifs (ITAMs) located within the intracellular domains of the associated CD3 complex[58]. These ITAMs are phosphorylated by Src family kinases, setting off a signaling cascade that involves key molecules such as ZAP-70 and phospholipase C (PLC). This cascade results in the generation of second messengers—including calcium ions (Ca^{2+}), diacylglycerol (DAG), and inositol trisphosphate (IP_3)—and activates the Ras pathway. Together, these signals promote the activation of transcription factors like NF-κB, AP-1, and NFAT, ultimately leading to the transcriptional changes necessary for full T cell activation.

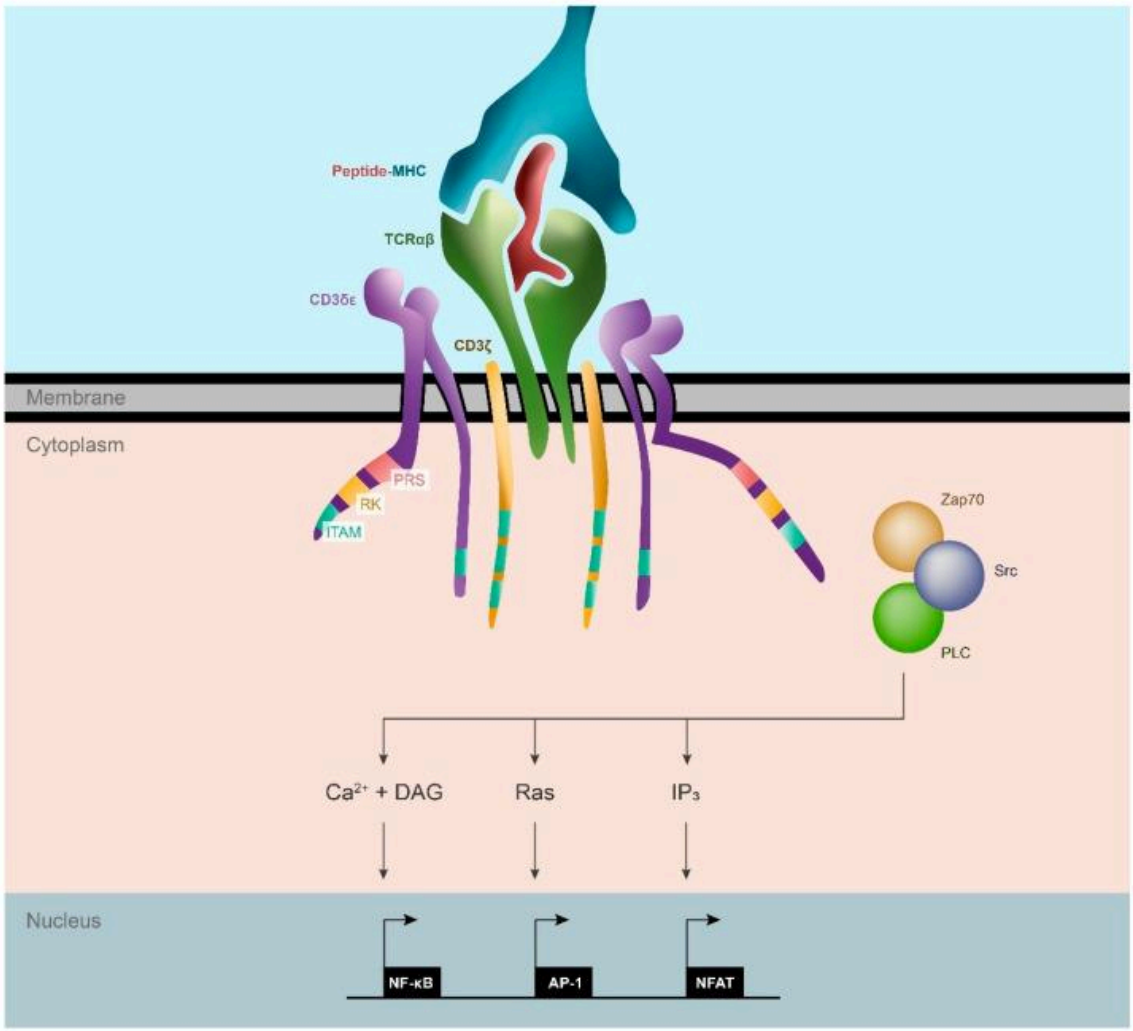
Beyond initiating activation, CD3 signaling plays an important regulatory role in T cell development and homeostasis[59]. During thymic selection, appropriate signaling through the CD3/TCR complex determines whether developing T cells will survive and mature. Weak signaling leads to death by neglect, strong self-reactive signaling leads to negative selection (deletion), and moderate signaling allows for positive selection. In the periphery, CD3 signaling thresholds help maintain immune tolerance, determining whether T cells become activated, enter an anergic state (non-responsive), or undergo apoptosis. These regulatory checkpoints are essential for preventing inappropriate immune responses to self-antigens.

In autoimmune diseases, dysregulation of CD3-mediated signaling contributes to the breakdown of immune tolerance[60]. Hyperactivation of the CD3/TCR pathway can lead to exaggerated responses against self-antigens, driving chronic inflammation and tissue damage, as seen in diseases like type 1 diabetes, systemic lupus erythematosus, and multiple sclerosis. On the other hand, inadequate signaling during thymic development may fail to eliminate autoreactive T cells, allowing them to enter circulation and initiate autoimmunity. Thus, maintaining balanced CD3 signaling is crucial for both immune competence and self-tolerance.

Therapeutically, CD3 is a validated target for modulating the immune system in autoimmune conditions. Monoclonal antibodies targeting CD3, such as teplizumab, have shown promise in delaying the onset of type 1 diabetes in at-risk individuals. These agents do not fully activate T cells but instead induce partial signaling that promotes immune tolerance—either by inducing anergy or apoptosis in effector T cells or by expanding regulatory T cell populations.

[57] Liu D, Hu X, Chen Z, Wei W, Wu Y. Key links in the physiological regulation of the immune system and disease induction: T cell receptor -CD3 complex. *Biochem Pharmacol.* 2024 Sep;227:116441. doi: 10.1016/j.bcp.2024.116441. Epub 2024 Jul 17. PMID: 39029632.
[58] Menon AP, Moreno B, Meraviglia-Crivelli D, Nonatelli F, Villanueva H, Barainka M, Zheleva A, van Santen HM, Pastor F. Modulating T Cell Responses by Targeting CD3. *Cancers (Basel).* 2023 Feb 13;15(4):1189. doi: 10.3390/cancers15041189. PMID: 36831533; PMCID: PMC9953819.
[59] Shah, K., Al-Haidari, A., Sun, J. et al. T cell receptor (TCR) signaling in health and disease. *Sig Transduct Target Ther* 6, 412 (2021). https://doi.org/10.1038/s41392-021-00823-w
[60] Menon AP, Moreno B, Meraviglia-Crivelli D, Nonatelli F, Villanueva H, Barainka M, Zheleva A, van Santen HM, Pastor F. Modulating T Cell Responses by Targeting CD3. *Cancers (Basel).* 2023 Feb 13;15(4):1189. doi: 10.3390/cancers15041189. PMID: 36831533; PMCID: PMC9953819.

Figure 11: CD3 Function in T Cell Activation



Source: Menon et al., 2023

CD3 in Multiple Sclerosis

In the context of MS, particularly SPMS, CD3 expression on T cells has emerged as a potentially critical modulator of disease progression.

Researchers found significant heterogeneity in CD3 levels specifically on $CD28^+$ $CD4^+$ T cells among patients with SPMS[61]. This variation was not merely incidental—it correlated with distinct clinical trajectories, suggesting that CD3 expression could serve as a biomarker for disease severity or progression rate. More importantly, the study identified a mechanistic interaction between CD3 levels and human herpesvirus 6 (HHV-6), a virus previously implicated in MS pathophysiology. Elevated or dysregulated CD3 expression appeared to be associated with higher HHV-6 activity, which in turn could contribute to heightened immune activation and inflammation within the central nervous system. This link implies that HHV-6 may exacerbate neuroinflammatory processes in MS by modulating CD3 levels on T cells, potentially tilting immune responses toward a more pathogenic phenotype.

In MS, particularly in both relapsing and progressive forms, an unusual subset of T cells that co-express CD3 and CD20 ($CD3^+CD20^+$ T cells) has gained increasing attention for their potential role in disease pathogenesis[62]. These cells are found in higher abundance in the cerebrospinal fluid (CSF) and within CNS lesions of MS patients. Unlike typical T cells, these $CD3^+CD20^+$ cells display cytotoxic properties, including the expression of perforin and granzymes—suggesting they may directly contribute to neural tissue damage. Their presence correlates with higher disease activity and chronic progression, implying that $CD3^+CD20^+$ T cells are not merely bystanders but active players in autoimmune inflammation. Notably, these cells are thought to bridge innate and adaptive immunity by behaving more aggressively than conventional T cell subsets.

The clinical importance of this subset is highlighted by the effectiveness of anti-CD20 therapies (such as ocrelizumab, rituximab, and ublituximab), which target not only B cells but also deplete $CD3^+CD20^+$ T cells. The therapeutic benefit observed in MS patients receiving these monoclonal antibodies may therefore stem in part from the removal of this pro-inflammatory T cell population.

CD3 as a Therapeutic Target of MS

Anti-CD3 therapies are being developed in MS despite the widespread use and success of anti-CD20 treatments because they offer a fundamentally different mechanism of action and broader immunomodulatory potential[63]. Furthermore, not all patients respond adequately to anti-CD20 treatments. Some develop resistance, immune-related adverse events, or continued disease progression despite B-cell depletion. While anti-CD20 therapies like ocrelizumab and ofatumumab deplete B cells and some $CD20^+$ T cells, they do not address the broader population of autoreactive T cells—particularly $CD4^+$ Th1 and Th17 subsets—that play a central role in MS pathogenesis. CD3, on the other hand, is a component of the T-cell receptor complex expressed on all mature T cells, making it a more comprehensive target for modulating T cell–driven autoimmunity. Anti-CD3 therapies may offer an alternative or complementary approach for these patients.

Anti-CD3 monoclonal antibodies (e.g., teplizumab, otelixizumab) have demonstrated the ability not only to suppress autoreactive T cells but also to induce immune tolerance by expanding Tregs and altering cytokine profiles[64]. This approach has been shown to dampen immune overactivation without complete immune ablation, distinguishing it from the depletion strategies of anti-CD20 therapies. Such modulation is particularly appealing for progressive or treatment-resistant forms of MS, where B-cell targeting alone may be insufficient. There is also potential for combining anti-CD3 with anti-CD20 therapies to simultaneously target both T and B cell axes, which may yield synergistic clinical benefits.

[61] Cao L, Chen C, Pi W, Zhang Y, Xue S, Yong VW, Xue M. Immune mechanisms in multiple sclerosis: CD3 levels on CD28+ CD4+ T cells link antibody responses to human herpesvirus 6. *Cytokine.* 2025 Mar;187:156866. doi: 10.1016/j.cyto.2025.156866. Epub 2025 Jan 29. PMID: 39884183.
[62] Arneth B. Current Knowledge about CD3+CD20+ T Cells in Patients with Multiple Sclerosis. *Int J Mol Sci.* 2024 Aug 18;25(16):8987. doi: 10.3390/ijms25168987. PMID: 39201672; PMCID: PMC11354236.
[63] Huang H, Wei X. Therapeutic potential of CD20/CD3 bispecific antibodies in the treatment of autoimmune diseases. *Rheumatol Immunol Res.* 2025 Jan 9;5(4):209-216. doi: 10.1515/rir-2024-0029. PMID: 39802547; PMCID: PMC11720466.
[64] Kuhn C, Weiner HL. Therapeutic anti-CD3 monoclonal antibodies: from bench to bedside. *Immunotherapy.* 2016 Jul;8(8):889-906. doi: 10.2217/imt-2016-0049. Epub 2016 May 10. PMID: 27161438.

Limitation of Current Anti-CD3 Therapies for Treating MS

Current anti-CD3 therapies for treating MS face several important limitations, which have thus far restricted their clinical adoption and success compared to more established options like anti-CD20 agents[65].

Safety and Cytokine Release Syndrome (CRS). Anti-CD3 monoclonal antibodies (e.g., OKT3, teplizumab, otelixizumab) can trigger cytokine release syndrome, especially when given in higher doses. Anti-CD3 monoclonal antibodies (mAbs) can paradoxically induce CRS despite their long-term goal of immunosuppression. This occurs because CD3 is a central component of the TCR complex, and anti-CD3 mAbs—especially when first administered—can strongly activate T cells, leading to rapid release of proinflammatory cytokines such as IL-2, IFN-γ, and TNF-α. This "first-dose effect" results in systemic inflammation, presenting as fever, hypotension, and flu-like symptoms characteristic of CRS.

Broad Immunosuppression. CD3 is expressed on all mature T cells, not just the pathogenic autoreactive subsets. Thus, anti-CD3 therapy may non-selectively suppress the entire T cell population, risking opportunistic infections or reactivation of latent viruses (e.g., EBV, JC virus), particularly concerning in MS where patients may already be on other immunomodulatory agents.

BBB Permeability. Most conventional anti-CD3 monoclonal antibodies do not effectively cross the blood-brain barrier (BBB) under normal physiological conditions. Their limited BBB permeability remains a barrier for direct CNS effects for treating neurodegenerative diseases.

Mechanism of Action – Foralumab

Foralumab is a fully human anti-CD3 monoclonal antibody being developed for autoimmune and neuroinflammatory diseases, notably MS, with a unique intranasal route of administration (Figure 12). Unlike traditional systemic anti-CD3 therapies given intravenously (IV),foralumab's intranasal delivery targets the mucosal immune system, inducing regulatory immune responses without causing broad immunosuppression CRS.

Foralumab binds to the CD3ε subunit of the TCR complex on T lymphocytes. However, when administered via the nasal mucosa, the immune response is fundamentally different from systemic anti-CD3 antibodies.

Induction of Tregs. Intranasal foralumab promotes the generation and expansion of Tregs (particularly IL-10-producing or FOXP3+), which help suppress autoreactive effector T cells that drive inflammation in autoimmune diseases like MS.

Immune Tolerization without T-cell Depletion. Unlike systemic CD3 antibodies, which often result in T-cell activation, depletion, or redistribution, mucosal foralumab induces immune tolerance. It modulates T cell function rather than killing or depleting T cells, preserving broader immune integrity.

Reduced Inflammatory Cytokine Signaling. foralumab downregulates pro-inflammatory pathways, including interferon signaling, and reduces expression of genes linked to T cell activation (e.g. NKG7, CCL5), shifting the immune balance toward a regulatory phenotype.

Non-invasive and patient friendly. Intranasal foralumab avoids the need for injections or infusions, making it more suitable for long-term or outpatient use, especially in chronic diseases like MS.

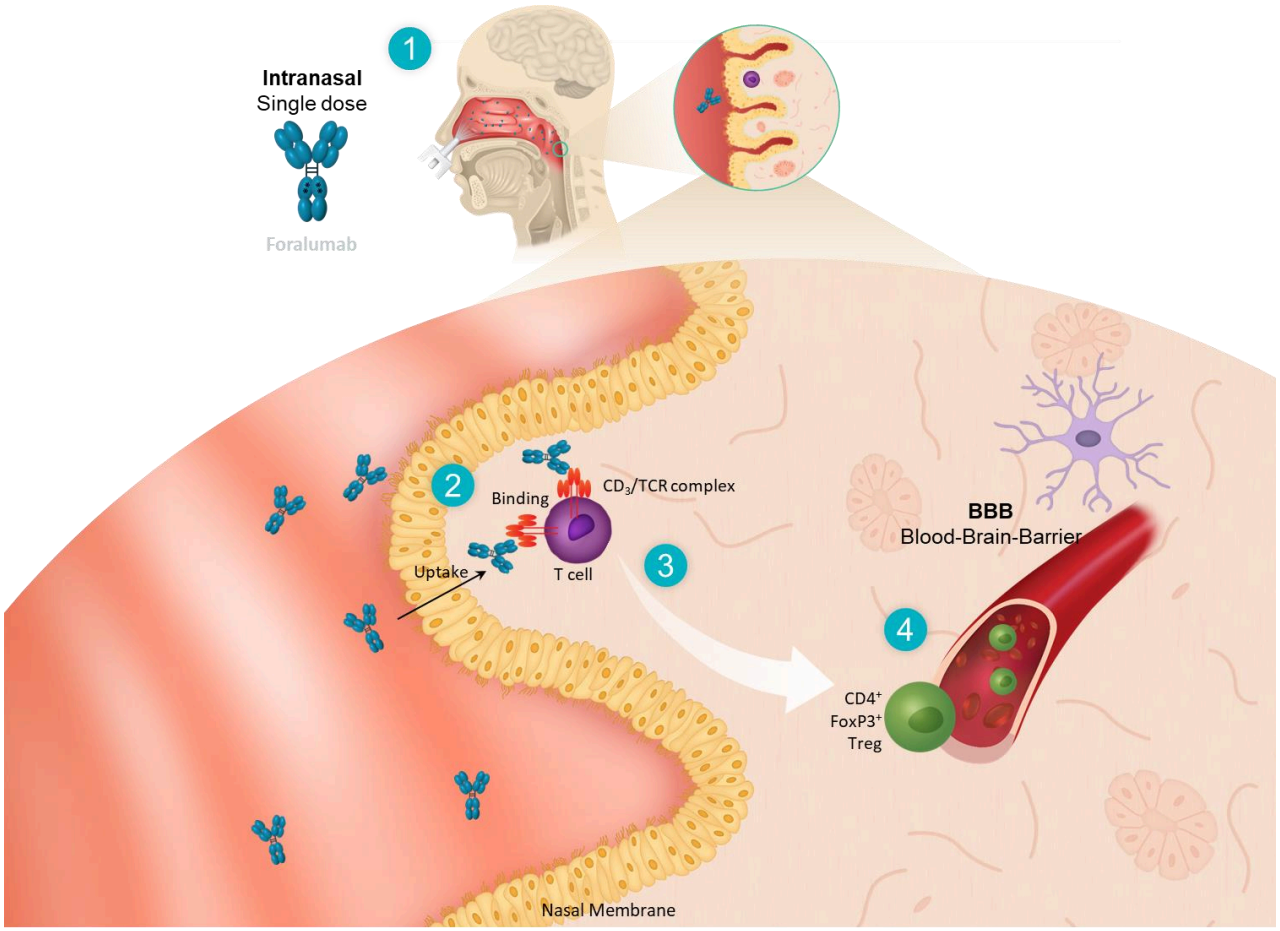
Targeting mucosal immune pathways. foralumab stimulates mucosal-associated lymphoid tissue (MALT), particularly in the nasal cavity, a key site for immune tolerization and regulatory T cell induction.

Avoids Systemic Toxicity and CRS. Intranasal delivery of foralumab bypasses systemic circulation, significantly reducing the risk of cytokine release syndrome, which is a major concern with IV anti-CD3 therapies.

Potential CNS Effects via Nasal–Brain Pathway. There is emerging evidence that intranasal delivery may provide limited direct access to the CNS via the olfactory and trigeminal pathways, potentially modulating CNS inflammation locally in diseases like MS.

[65] Kuhn C, Weiner HL. Therapeutic anti-CD3 monoclonal antibodies: from bench to bedside. *Immunotherapy.* 2016 Jul;8(8):889-906. doi: 10.2217/imt-2016-0049. Epub 2016 May 10. PMID: 27161438.

Figure 12: Foralumab - Mechanism of Action



Source: Tiziana Life Science Corporate Presentation, June 2025

CLINICAL DEVELOPMENT OF FORALUMAB

Prior Clinical Trials Using Intravenous and Oral Foralumab

Before its current focus on intranasal delivery, foralumab was explored in both intravenous (IV) and oral forms. These early studies provided foundational insights into its immunological potential but also revealed limitations that ultimately led Tiziana Life Sciences to pivot toward intranasal administration, especially for treating neuroinflammatory and neurodegenerative diseases.

In its initial development as an IV therapy (then called NI-0401), foralumab was tested in a Phase 1/2 trial in patients with moderate to severe Crohn's disease. The study used escalating doses (up to 1mg/day for five days), and the drug was generally well tolerated at those levels. However, higher doses (2mg and above) were associated with infusion-related reactions, including cytokine release and Epstein-Barr virus (EBV) reactivation, likely due to systemic T-cell activation. Immunologically, IV foralumab caused transient lymphopenia and reduced CD3 expression on the surface of T cells—a known effect of systemic anti-CD3 therapy. Despite these immune shifts, the clinical efficacy was underwhelming. While some reduction in endoscopic scores was observed at the 1mg dose, there was no significant improvement in the Crohn's Disease Activity Index (CDAI), the primary efficacy endpoint. These results suggested that while the IV form had potent systemic immune effects, it lacked therapeutic benefit in Crohn's disease and carried safety risks that made chronic use undesirable.

The oral formulation of foralumab was then developed with the goal of achieving mucosal (gut-localized) immunomodulation while avoiding systemic exposure. Enteric-coated capsules were tested in a Phase 1 study in healthy volunteers, showing excellent tolerability across doses ranging from 1.25 to 5mg. Animal studies and prior human data (including earlier oral anti-CD3 studies with mouse antibodies like OKT3) had indicated that oral anti-CD3 can induce regulatory T cells (Tregs) in the gut, which might help reduce inflammation in diseases like ulcerative colitis and Crohn's. However, when Tiziana initiated a Phase 1b trial in Crohn's patients in early 2022, the study encountered significant recruitment barriers—partly due to COVID-related hospitalization protocols that required patients to remain in-patient for up to 14 days. Even after the trial was amended to shorten hospitalization and reduce the number of treatment days, recruitment remained difficult. Eventually, the program was paused as the company reassessed its strategy.

Shift Towards Intranasal Foralumab in CNS Indications

What shifted the landscape was the emerging data from preclinical models and early human studies showing that intranasal administration of foralumab could drive regulatory immune responses without systemic T-cell depletion or EBV activation. In preclinical studies, nasal anti-CD3 modulated CNS inflammation through mucosal immune signaling, leading to improvements in animal models of progressive multiple sclerosis, Alzheimer's disease, and other autoimmune conditions. Importantly, this route of delivery allowed for immune modulation without CD3 receptor downregulation or systemic cytokine release—a key differentiator from the IV route.

A landmark Phase 1 trial in healthy human volunteers using intranasal foralumab (at doses of 10, 50, and 250µg) demonstrated excellent tolerability and no systemic side effects[66]. The 50µg dose emerged as the optimal immunologic dose. Flow cytometry and single-cell RNA sequencing revealed that nasal foralumab increased regulatory T cell markers such as LAP, TIGIT, and KLRG1, while reducing pro-inflammatory cytokines like IFN-γ, IL-17, and TNFα. There was also a reduction in cytotoxic CD8+ effector-memory T cells, and an increase in naïve T cell populations, indicating a broad anti-inflammatory immune reset. Furthermore, scRNA-seq revealed gene expression changes in monocytes and memory CD4+ T cells consistent with an anti-inflammatory, tolerogenic shift.

These findings prompted Tiziana to pivot fully toward intranasal delivery, especially for CNS conditions where chronic inflammation plays a major role. Pilot studies in progressive multiple sclerosis and even in COVID-19 (which involves cytokine-driven inflammation) confirmed the safety and biological activity of intranasal foralumab. Unlike oral or IV routes, the intranasal approach allowed access to the nasopharynx-associated lymphoid tissue (NALT), which is closely linked to immune signaling pathways affecting the brain. The ability to safely induce immune regulation through this mucosal route, without causing systemic T cell depletion or triggering viral reactivation, made intranasal foralumab a uniquely promising candidate for neurodegenerative and autoimmune disorders.

[66] Chitnis T, Kaskow BJ, Case J, Hanus K, Li Z, Varghese JF, Healy BC, Gauthier C, Saraceno TJ, Saxena S, Lokhande H, Moreira TG, Zurawski J, Roditi RE, Bergmark RW, Giovannoni F, Torti MF, Li Z, Quintana F, Clementi WA, Shailubhai K, Weiner HL, Baecher-Allan CM. Nasal administration of anti-CD3 monoclonal antibody modulates effector CD8+ T cell function and induces a regulatory response in T cells in human subjects. *Front Immunol.* 2022 Nov 23;13:956907. doi: 10.3389/fimmu.2022.956907. PMID: 36505477; PMCID: PMC9727230.

Open-Label Study of Nasal Foralumab in Non-Active Secondary Progressive MS

Study Design. The study was an open-label, single-arm pilot trial designed to evaluate the safety, tolerability, and immunologic effects of intranasal foralumab in patients with non-active secondary progressive multiple sclerosis (na-SPMS) who were experiencing progression independent of relapse activity (PIRA), despite prior B-cell therapy[67]. Ten participants were enrolled and received intranasal doses of foralumab at 50µg, administered three times per week (Monday, Wednesday, Friday) for two weeks, followed by one week off—forming a three-week treatment cycle. This cycle was repeated continuously for at least six months, with some patients continuing treatment beyond 12 months.

The primary outcomes focused on safety and clinical stabilization, assessed through monitoring of adverse events and changes in the Expanded Disability Status Scale (EDSS). Neuroimaging assessments included MRI scans to track new T2 lesion development and F18-TSPO PET imaging to evaluate microglial activation in the brain. Additionally, the study utilized mGALP PET imaging to correlate fatigue severity with hippocampal microglial activity, and fatigue was systematically measured using the Modified Fatigue Impact Scale (MFIS).

Immune profiling was a key component of the study, with single-cell RNA sequencing (scRNA-seq) used to analyze peripheral blood samples. This enabled researchers to track immunologic shifts, including increases in Tregs) and upregulation of anti-inflammatory markers like TGF-β across various immune cell types. Overall, the design integrated clinical, imaging, and molecular endpoints to capture a comprehensive picture of how nasal foralumab might modulate disease progression, inflammation, and symptom burden in SPMS.

Safety Data. Intranasal foralumab was well tolerated across all participants. There were no serious or severe treatment-related adverse events reported during the treatment period. Patients did not experience infusion-related reactions, systemic immune suppression, or viral reactivation—issues previously seen with intravenous anti-CD3 therapies. This favorable safety profile supports the use of nasal delivery as a non-invasive and low-risk approach for long-term treatment in progressive multiple sclerosis.

Efficacy Data. Ten patients received at least six months of treatment, with all showing either clinical improvement or disease stabilization. Measures included EDSS (a standard disability score), pyramidal function, walking speed (T25FW), and fatigue (MFIS).

Over the six-month treatment period, none of the participants experienced worsening of their Expanded EDSS scores (Figure 13A). Notably, among the four patients who continued treatment for twelve months, three showed improvement in their EDSS scores, suggesting that longer-term use of nasal foralumab may not only halt progression but potentially reverse some neurologic decline.

Fatigue, a common and debilitating symptom in SPMS, also improved in a majority of patients (Figure 13B). Notably, fatigue scores improved in 70% of patients. Using the Modified Fatigue Impact Scale (MFIS), seven out of ten patients reported meaningful reductions in fatigue severity during the treatment period. Furthermore, baseline MFIS scores were strongly correlated with hippocampal microglial activity measured by mGALP PET imaging (correlation coefficient r=0.89, p=0.007), implying that patients with greater neuroinflammation experienced more fatigue—and that this may be reversible through anti-inflammatory intervention with foralumab.

Neuroimaging using F18-TSPO PET scans demonstrated a statistically significant reduction in microglial activation after six months of treatment (Figure 13C). Microglial activation is a known driver of neurodegeneration in SPMS, and its reduction indicates a potential disease-modifying effect of foralumab. Importantly, MRI scans showed no new T2 lesions during the study period, reinforcing the observation that nasal foralumab helped maintain a stable state disease without new inflammatory activity in the brain. PET scans measuring White Matter Z-scores, used as a marker of microglial activation and brain inflammation, showed a median 36% reduction, with five out of six patients exhibiting clear improvements (Figure 13D). Reductions in inflammation ranged from 28% to 48%, indicating a robust anti-inflammatory effect of foralumab at the neuroimmune level.

A standout case, patient EA2, had previously experienced worsening disability despite treatment with ocrelizumab, with their EDSS rising from 3.5 to 6.0 and needing a cane to walk. After beginning foralumab in early 2022, EA2 saw progressive improvement: walking unaided, regaining functional mobility, and ultimately returning to full-time work by 2023. These

[67] Atimano, J. R., *et al.,* (2025). Nasal foralumab treatment of PIRA induces regulatory immunity, dampens microglial activation and stabilizes clinical progression in non-active secondary progressive multiple sclerosis (na-SPMS). *medRxiv.* https://doi.org/10.1101/2025.04.30.25326602

outcomes illustrate foralumab's potential to reverse functional decline in patients who had previously exhausted standard therapies.

Finally, immune profiling using single-cell RNA sequencing revealed early and sustained immunologic changes consistent with regulatory immune activation. Specifically, there was an increase in circulating regulatory T cells (Tregs), along with heightened expression of TGF-β across multiple immune cell populations. These findings support the proposed mechanism of action for nasal foralumab: inducing systemic and CNS immune tolerance without depleting T cells, thus promoting long-term stabilization in neurodegenerative disease.

Figure 13: Efficacy Data from Open-Label Study of Nasal Foralumab in Non-Active Secondary Progressive MS

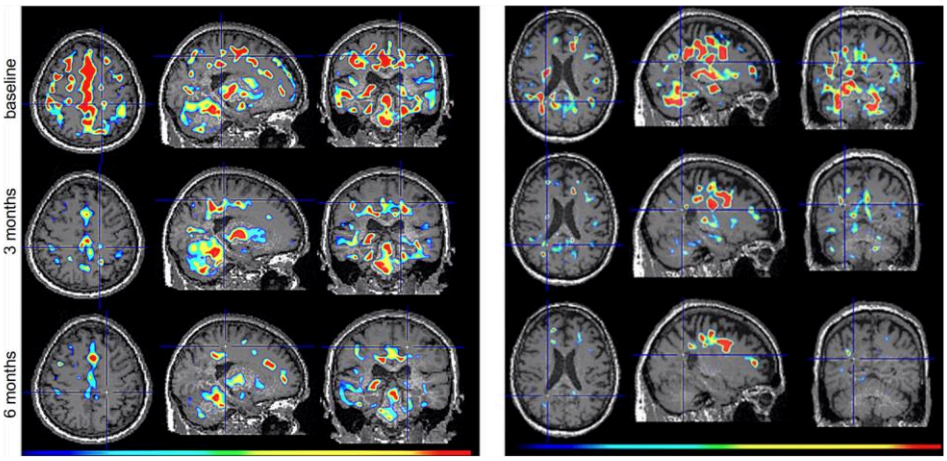
A

Subject	Sex	Age at treatment start	Race	Ethnicity	Last MS Treatment	Treatment Start	Dosing cycles completed	Baseline EDSS	6-month EDSS	6 month Change	12 month EDSS	12 month change
1	M	60-65	White	Non-HL	Ocrevus 12/2020	05/2021	21	6.0	6.0	0		
2	M	40-45	White	Non-HL	Ocrevus 10/2021	01/2022	38	6.0	6.0	0	5.5	-0.5
3	F	65-70	White	Non-HL	Ocrevus 04/2022	01/2023	28	6.5	6.5	0		
4	M	50-55	White	Non-HL	Ocrevus 12/2020	12/2022	23	2.5	2.0	-0.5		
5	F	60-65	White	Non-HL	Ocrevus 01/2022	01/2023	28	6.0	6.0	0		
6	F	55-60	U/NR	NR	Ocrevus 11/2021	01/2023	8	6.0	6.0	0		
7	F	60-65	White	Non-HL	Ocrevus 06/2023	09/2023	22	6.5	6.5	0	6.5	0
8	F	60-65	White	Non-HL	Rituxan 02/2023	08/2023	23	3.5	3.0	-0.5	2.5	-1.0
9	M	60-65	White	Non-HL	No DMT	09/2023	18	4.5	3.5	-1.0	3.5	-1.0
10	M	40-45	Black	Non-HL	Ocrevus 03/2023	10/2023	13	6.5	6.5	0		

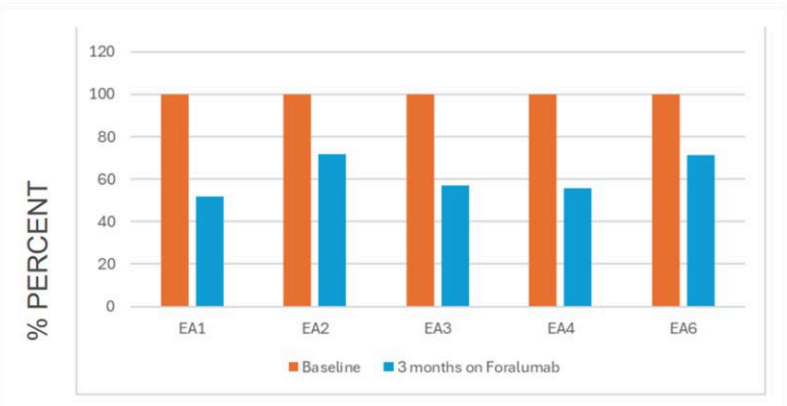
B

	EDSS	Pyramidal score	T25FW	MFIS
EA1	–	↓	–	–
EA2	↓	–	↓	↓
EA3	–	–	↓	–
EA4	↓	–	–	↓
EA5	–	↓	↓	↓
EA6	–	–	–	↓
EA7	–	–	↓	↓
EA8	↓	↓	–	↓
EA9	↓	–	–	↓
EA10	–	↓	–	–

C



D



Source: Atimano et al., 2025

Phase 2a Study Design in Non-Active Secondary Progressive MS

Part One. This is a Phase 2a, randomized, double-blind, placebo-controlled clinical trial (TILS-021) investigating the safety, tolerability, and biological activity of intranasal foralumab in patients with na-SPMS (Figure 14). The study focuses on its potential to reduce microglial activation in the brain, a key driver of disease progression in na-SPMS, where effective treatment options are limited.

The trial plans to enroll ~55 adults aged 18 to 75 with confirmed non-active SPMS and an Expanded Disability Status Scale (EDSS) score between 2.5 and 6.5. Participants will be randomized equally into three parallel arms: Group A will receive 50µg of intranasal foralumab, Group B will receive 100µg, and Group C will receive a placebo (acetate buffer). The dosing schedule consists of three administrations per week for two weeks followed by one week off, repeated across four cycles (12 weeks total).

Primary endpoints include safety and tolerability (adverse events), changes in microglial activation as measured by [^{18}F]PBR06 PET imaging, and changes in the Total Nasal Symptom Score (TNSS). The study is being conducted across six major US academic sites, including Yale, Johns Hopkins, Brigham and Women's, UMass, Weill Cornell, and Thomas Jefferson. The trial began screening patients in November 2023, and the estimated primary completion date is 1Q26. It is currently recruiting and has received FDA Fast Track designation.

Part Two. This Phase 2 open-label extension study (TILS-022) is designed to evaluate the safety, tolerability, and exploratory efficacy of intranasal foralumab in patients with na-SPMS. The trial includes participants who have completed the prior randomized, placebo-controlled dose-ranging study (TILS-021). Its purpose is to allow continued treatment with foralumab while collecting additional long-term safety and biomarker data in a real-world setting.

The trial plans to enroll approximately 55 participants, aged 18 to 75, all of whom must have completed the TILS-021 study and meet continuation criteria. Each participant will begin treatment with a 50µg dose of foralumab, administered intranasally three times per week—on Mondays, Wednesdays, and Fridays — for two consecutive weeks, followed by a one-week treatment break. This three-week cycle will be repeated throughout the six-month treatment period.

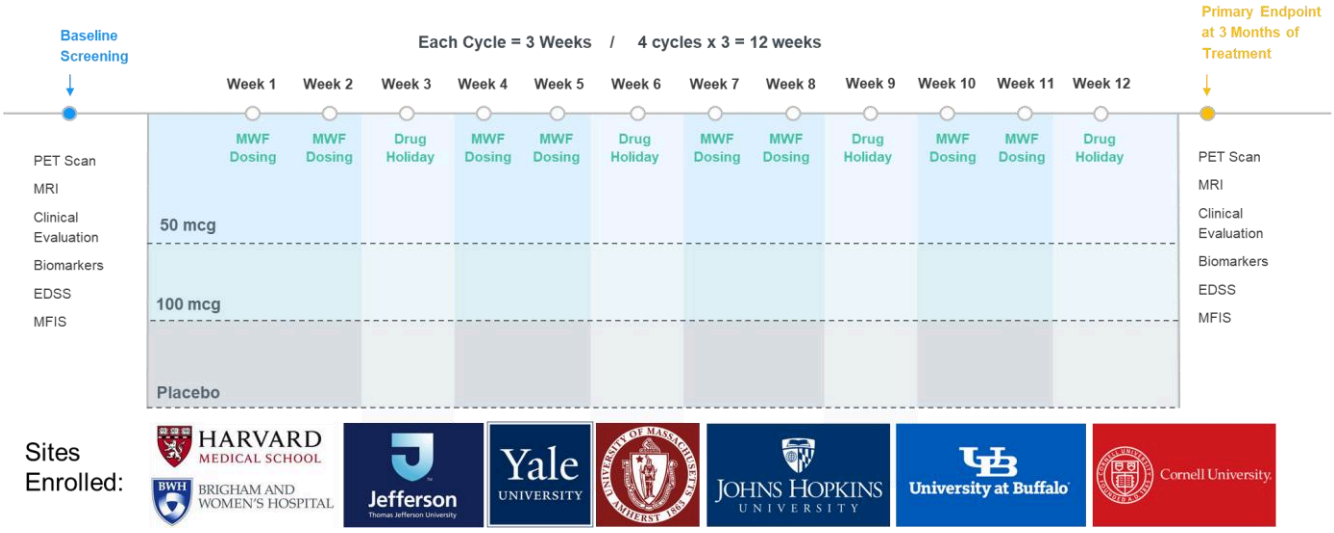
A key feature of this study is the possibility of dose escalation. At Week 12, patients who meet predefined clinical criteria will be eligible to increase their dose to 100µg, enabling a flexible approach to balancing efficacy and tolerability on a per-patient basis. This individual dose adjustment component is important for understanding patient variability in response to foralumab and for optimizing the therapeutic window.

Throughout the study, patients will undergo comprehensive safety assessments, including physical exams, laboratory tests (hematology, chemistry), nasal examinations, and scoring of nasal symptoms using the Total Nasal Symptom Score (TNSS). In addition, the study will evaluate fatigue symptoms using the MFIS, a critical measure in SPMS where fatigue is a major contributor to disability and quality-of-life decline.

For exploratory efficacy and mechanistic analysis, the study includes MRI to monitor lesion burden and brain volume changes, as well as PET imaging using TSPO ligands to assess changes in microglial activation, a marker of central nervous system inflammation. Blood samples will also be collected for immune biomarker analysis, with a focus on regulatory T cells and cytokine profiles, to evaluate foralumab's immunomodulatory effects over time.

The trial officially began on March 4, 2025, and is expected to reach its primary completion date by August 30, 2026. As an open-label extension, this study serves a dual purpose: it provides ongoing access to foralumab for patients previously enrolled in the double-blind trial, while also generating longitudinal data on safety, immune engagement, and potential slowing of disease progression in a real-world clinical setting.

Figure 14: Phase 2a Study Design in Non-Active Secondary Progressive MS



Source: Tiziana Life Science Corporate Presentation, June 2025

Case Study of Moderate Alzheimer's Disease with Intranasal Foralumab

The company reported a case study involving a 78-year-old man with moderate AD who received intranasal foralumab[68]. This treatment was provided under the FDA's expanded-access program, and its effects were monitored using 18F-PBR06 PET, a second-generation tracer that targets TSPO (a marker of activated microglia). This marks the first reported use of 18F-PBR06 PET in a human Alzheimer's patient to assess neuroinflammation after intranasal foralumab treatment.

Three months after the start of therapy, PET imaging showed a global reduction in microglial activation across the brain (Figure 15A & B). The decline was particularly notable in areas commonly affected by Alzheimer's pathology, such as the precuneus, posterior cingulate, and anterior cingulate cortices—regions typically associated with a high amyloid burden (Figure 15C & D). These findings suggest that foralumab may be exerting an anti-inflammatory or immunomodulatory effect by dampening microglial activity, which is increasingly recognized as a contributor to disease progression in Alzheimer's.

The report builds on prior findings where nasal foralumab demonstrated a capacity to reduce microglial activation in both animal models of AD and patients with secondary progressive multiple sclerosis. The mechanism is thought to involve modulation of T-cell activity and systemic immune response, leading to reduced neuroinflammation without the need for systemic immunosuppression. This approach could offer a non-invasive and potentially safer alternative to traditional systemic immunotherapies.

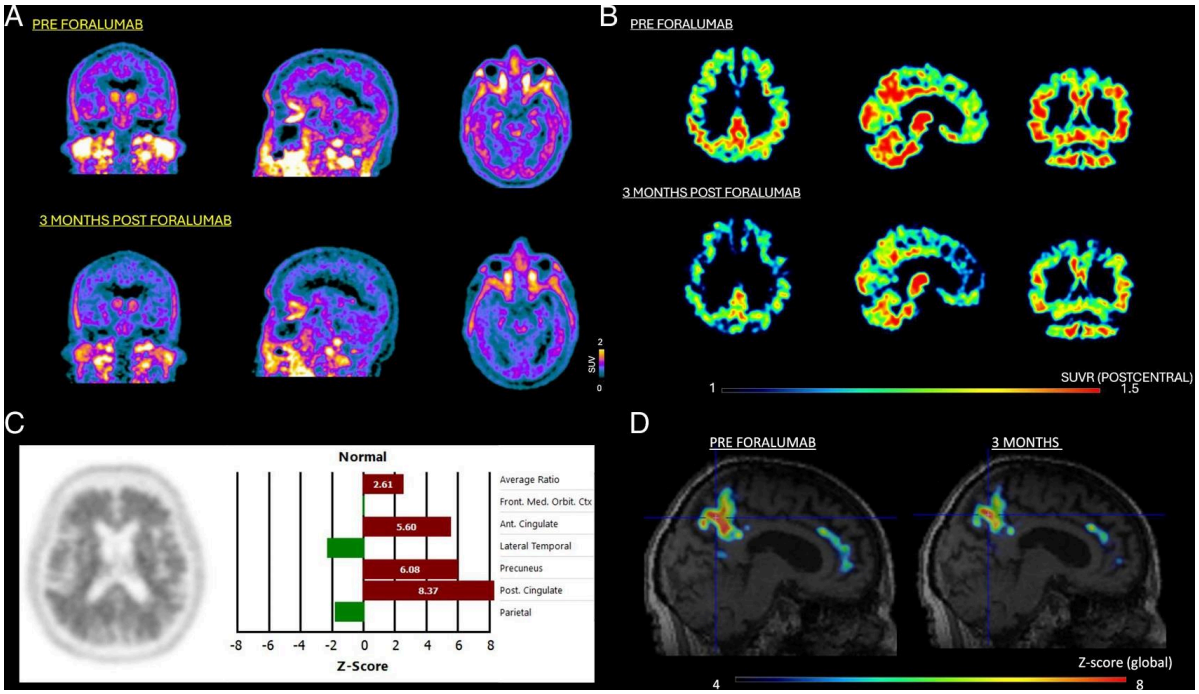
Analysis of the patient's white blood cells before and after treatment showed strong immune-modulating effects, with notable changes in CD4 and CD8 T cells, as well as monocytes. These changes support imaging results from microglia PET scans taken at the same time, which showed a significant reduction in brain inflammation, indicating a connection between foralumab's immune impact and reduced neuroinflammation. Researchers also observed an increase in markers related to phagocytosis in classical monocytes, suggesting that intranasal foralumab may improve their capacity to clear amyloid plaques. This unexpected finding could point to a dual therapeutic role for the drug in Alzheimer's, addressing both inflammation and amyloid buildup.

The treatment was also well tolerated, with no side effects reported. Motivated by these encouraging results and the behavioral improvements noted by the patient's family, the patient and his wife have decided to extend the intranasal foralumab therapy for another six months. Importantly, this case has prompted the launch of a Phase 2a clinical trial (NCT06489548) to evaluate nasal foralumab in a broader cohort of patients with mild AD. If validated, foralumab could be used alongside other treatments targeting amyloid or tau, addressing the inflammatory component of the disease.

In summary, this case study provides early but compelling evidence that intranasal foralumab can reduce microglial activation in AD. It opens a new avenue for immunomodulatory treatment that targets neuroinflammation, potentially complementing existing approaches focused on amyloid and tau pathology.

[68] Singhal T, Cicero S, Gale SA, Horan N, Dubey S, Marshall GA, Weiner HL. Dampening of Microglial Activation With Nasal Foralumab Administration in Moderate Alzheimer's Disease Dementia. *Clin Nucl Med.* 2025 Aug 1;50(8):756-757. doi: 10.1097/RLU.0000000000005955. Epub 2025 May 13. PMID: 40359013; PMCID: PMC12208394.

Figure 15: Case Study of Moderate AD with Intranasal Foralumab



Source: Singhal et al., 2025

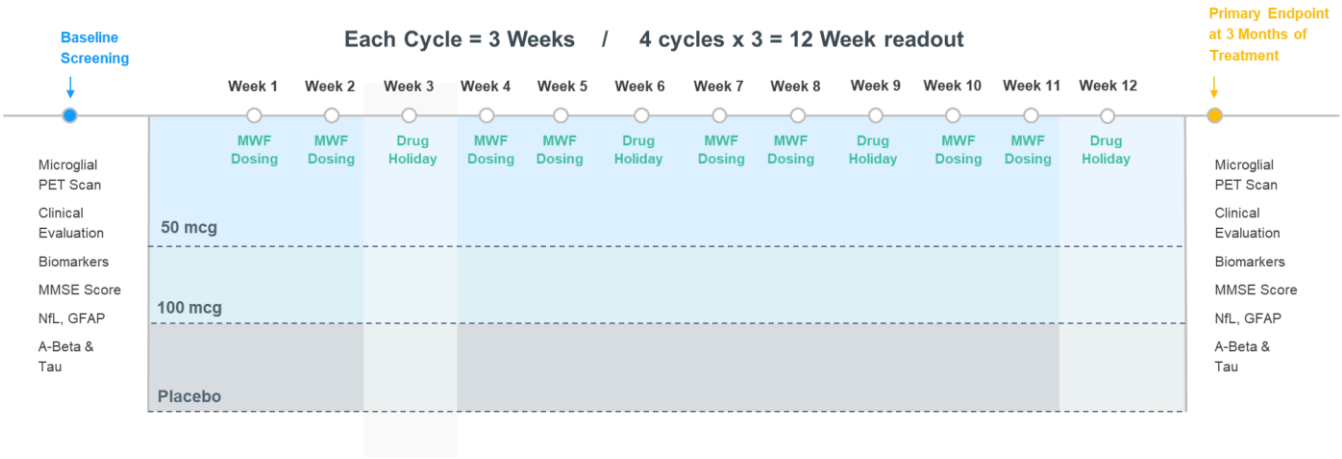
Phase 2a Study in Early Symptomatic AD

A Phase 2a clinical trial is currently underway to evaluate the potential of intranasal foralumab in treating patients with moderate AD. This study is focused on investigating the safety and efficacy of foralumab administered via the nasal route. The primary goal is to reduce neuroinflammation, a central factor contributing to the progression of Alzheimer's. To assess the drug's impact, the trial will monitor changes in microglial activation using PET imaging, along with various clinical parameters (Figure 16).

The trial is designed as a randomized, double-blind, placebo-controlled, multicenter study, incorporating a dose-ranging format to identify the optimal therapeutic window. It will evaluate key outcomes including safety and tolerability (based on adverse events), reductions in microglial activation observed through PET scans, and improvements in broader clinical measures such as disability progression, quality of life, and fatigue.

Preliminary evidence supporting this trial comes from an expanded access program, where ten participants with moderate AD showed either disease stabilization or improvement following nasal foralumab treatment. Based on these promising results, the FDA approved the enrollment of an additional 20 patients. In parallel, foralumab has also received Fast Track Designation from the FDA for the treatment of non-active secondary progressive multiple sclerosis, which may expedite its development and review for that condition.

Figure 16: Phase 2a Study Design in Early Symptomatic Alzheimer's Disease



Source: Tiziana Life Science Corporate Presentation, June 2025

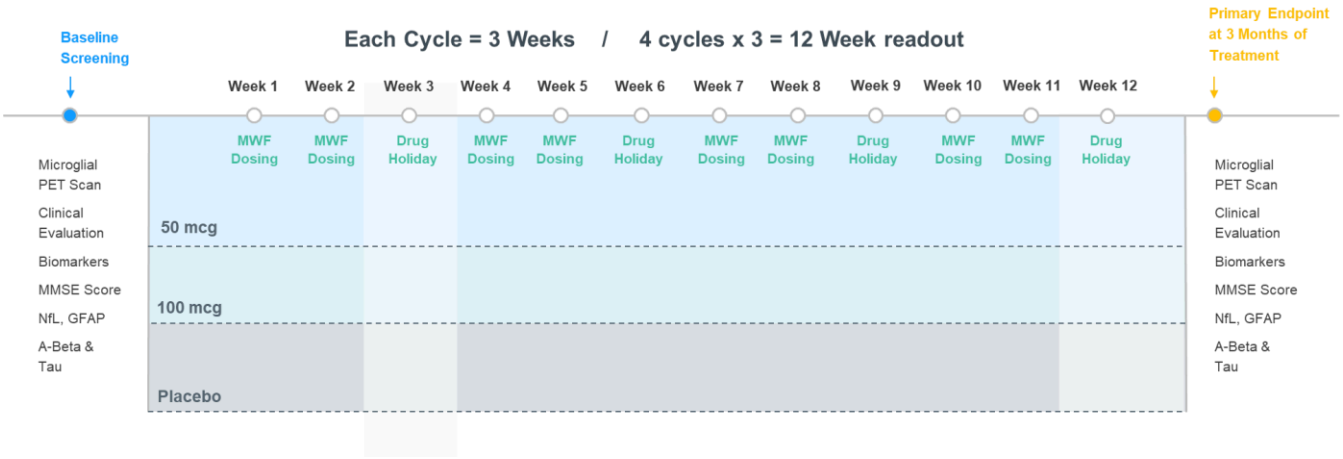
Phase 2a Study in ALS

The company has filed an IND application with the FDA to initiate a Phase 2 clinical trial of intranasal foralumab in patients with ALS. This move marks an expansion of the company's therapeutic focus beyond Alzheimer's disease and multiple sclerosis, into the ALS space. The trial is being supported by a grant from the ALS Association's Hoffman ALS Clinical Trial Awards Program.

The planned study will enroll 20 ALS patients and will assess two dosage levels of intranasal foralumab. The primary objectives are to evaluate safety and tolerability, while also exploring early signs of clinical benefit.

This initiative builds on earlier findings from both preclinical Alzheimer's models and clinical studies in multiple sclerosis, where intranasal foralumab has demonstrated an ability to reduce microglial activation and dampen neuroinflammation. These results provide a strong rationale for investigating its potential in ALS, a disease in which neuroinflammatory processes are increasingly recognized as key contributors to motor neuron damage.

Figure 17: Phase 2a Study Design in ALS



Source: Tiziana Life Science Corporate Presentation, June 2025

COMPETITIVE LANDSCAPE OF MS

Currently, there are 17 innovator drugs in Phase 2 or later clinical development for MS in the US and Europe, including small molecules, monoclonal antibodies, mRNA therapies, and cell therapies (Figure 18).

Figure 18: Candidate Drugs Under Clinical Development for Multiple Sclerosis

Drug	Company	Phase	Modality	MoA	Route of Administration	MS Category
SAR442168	Sanofi	NDA	Small Molecule	Bruton's Tyrosine Kinase (BTK) Inhibitor	Oral	MS
Remibrutinib	Novartis	Phase 3	Small Molecule	Bruton's Tyrosine Kinase (BTK) Inhibitor	Oral	RRMS
RG7845	Roche	Phase 3	Small Molecule	Bruton's Tyrosine Kinase (BTK) Inhibitor	Oral	RRMS
SAR441344	Sanofi	Phase 3	mAb	CD40L	IV	Non-Relapsing Secondary Progressive MS
Vidofludimus Calcium	Immunic	Phase 3	Small Molecule	Dihydroorotate Dehydrogenase (DHODH)	Oral	RRMS
Masitinib	AB Science	Phase 2/3	Small Molecule	Tyrosine Kinase Inhibitor	Oral	Progressive MS
MN-166	MediciNova	Phase 2b	Small Molecule	Glial attenuator	Oral	Progressive MS
BIIB091	Biogen	Phase 2	Small Molecule	Bruton's Tyrosine Kinase (BTK) Inhibitor	Oral	RRMS
CNM-Au8	Clene	Phase 2	Small Molecule	Myelin	Oral	RRMS & Progressive MS
HB-adMSC	Hope	Phase 2	Cellular	Immune System	IV	RRMS
KYV-101	Kyverna	Phase 2	Cellular	CAR-T	IV	Progressive MS
LY-3541860	Eli Lilly	Phase 2	mAb	CD19	IV	RRMS
mRNA-1195	Moderna	Phase 2	mRNA	Epstein Barr Virus (EBV)	IM	MS
NurOwn	BrainStorm	Phase 2	Cellular	Stem Cells	IM	MS
obexelimab	Zenas	Phase 2	mAb	CD19 & FcγRIIb	IV	Progressive MS
PIPE-307	JnJ	Phase 2	Small Molecule	Muscarinic M1 receptor	Oral	RRMS
TISCH Stem Cell	Tisch MS Research Center of New York	Phase 2	Cellular	Stem Cells	IV	Progressive MS

Source: BioMedTracker & Lucid Capital Markets Research

COMPETITIVE LANDSCAPE OF AD

Currently there are 21 innovator drugs under Phase 3 clinical development for Alzheimer's disease in the US and Europe, including 16 small molecules, three monoclonal antibodies, one recombinant peptide, and one cell therapy (Figure 19).

Figure 19: Candidate Drugs Under Phase 3 Clinical Development for Alzheimer's Disease

Drug	Company	Category	Modality	Mechanism of Action
ACP-204	Acadia	NME	Small Molecule	5-HT2A Receptor
Autologous Adipose-derived Stem Cells	CellTex	NME	Cell Therapy	Neurogeneration
Blarcamesine Hydrochloride	Anavex	NME	Small Molecule	NMDA Receptors
Buntanetap Tartrate	Annovis	NME	Small Molecule	Alpha Synuclein
Cromolyn Sodium + Ibuprofen	AZTherapies	NME	Small Molecule	Amyloid Beta
Dexmedetomidine	BioXcel	Non-NME	Small Molecule	Alpha 2A Adrenergic Receptor
Donanemab	Eli Lilly	NME	Monoclonal Antibody	Amyloid Beta
Etalanetug	Eisai	NME	Monoclonal Antibody	Tau
Fosgonimeton	Athira	NME	Small Molecule	HGF
Guanfacine Hydrochloride ER	Takeda	Non-NME	Small Molecule	Alpha 2A Adrenergic Receptor
Hydromethylthionine Mesylate	TauRx	NME	Small Molecule	Tau
Idalopirdine	Denovo	NME	Small Molecule	5-HT6 Receptor
Masitinib	AB Science	NME	Small Molecule	Tyrosine Kinase Inhibitor
Mirodenafil Dihydrochloride	AriBio	NME	Small Molecule	PDE5
Nabilone	Sunnybrook	NME	Small Molecule	CB1 Receptor
NE-3107	BioVie	NME	Small Molecule	MAP Kinase 1
NN-6535	Novo Nordisk	NME	Recombinant Peptide	GLP1R
Remternetug	Eli Lilly	NME	Monoclonal Antibody	Amyloid Beta
Simufilam Hydrochloride	Cassava	NME	Small Molecule	Filamin A
Tricaprilin	Cerecin	NME	Small Molecule	Cellular Metabolism
Valiltramiprosate	Alzheon	NME	Small Molecule	Amyloid Beta

Source: Global Data & Lucid Capital Markets Research

COMPETITIVE LANDSCAPE OF ALS

Besides the therapies approved for ALS (Figure 20), there are several drugs in development (Figure 21).

Figure 20: Marketed Drugs for ALS

Drug	Company	Target(s)	Modality	Route of Administration	US Approval Year
Rilutek (Riluzole)	ADVANZ PHARMA	Glutamine	Small Molecule	Oral	1995
Radicava (Edaravone)	Mitsubishi Tanabe	Mitochondria	Small Molecule	Oral / Intravenous	2017
Exservan (Riluzole Oral Film)	Mitsubishi Tanabe	Glutamine	Small Molecule	Sublingual Oral Transmucosal	2019
Relyvrio (Tauroursodeoxycholic Acid & Sodium Phenylbutyrate)	Amylyx	Mitochondria	Small Molecule	Oral	2022 (Withdrawn in 2024)
Qalsody (Tofersen)	Biogen	SOD1	Antisense	Intrathecal	2023
NEURONATA-R (Lenzumestrocel)	CORESTEM	Stem cells	Cell Therapy	Intrathecal	N/A (Approved in Korea only)

Source: BioMedTracker

Figure 21: Other Pipeline Drugs for ALS

Drug	Company	Addressable Patients	Target(s)	Compound	Phase
NurOwn	BrainStorm Cell Therapeutics	Both	Stem Cells	Cell Therapy	IIIb
ION363	Ionis	Familial ALS with FUS Mutation	FUS	Antisense	III
Masitinib	AB Science	Both	Tyrosine Kinase	Small Molecule	III
MN-166	MediciNova	Both	MIF, PDE10, PDE4	Small Molecule	II/III
SLS-005	Seelos Therapeutics	Both	TFEB	Small Molecule	II/III
CNM-Au8	Clene	Both	Mitochondrial Electron Transport Chain	Small Molecule	II/III
AL-001	Alector	Familial ALS C9orf72 Mutations	SORT1	mAbs	II
Albutein	Grifols	Both	Albumin	Protein	II
ALZT-OP1a	AZTherapies	Both	Mast Cell	Small Molecule	II
ANX-005	Annexon	Both	C1q & Complement Pathway	mAbs	II
AP-101	Neurimmune	Both	SOD1	mAbs	II
BLZ945	Novartis	Both	CSF-1R	Small Molecule	II
DNL788	Denali	Both	RIPK1	Small Molecule	II
EPI-589	Sumitomo	Both	Mitochondrial Electron Transport Chain	Small Molecule	II
LAM-002	AI Therapeutics	Familial ALS C9orf72 Mutations	PIKFYVE	Small Molecule	II
PTC857	PTC Therapeutics	Both	15-Lipoxygenase	Small Molecule	II
RNS60	Revalesio	Both	PI3K-Akt-BAD Pathway	Oxygenated Nanobubbles	II
Tegoprubart	Eledon	Both	CD40 / gp39, Fc Receptors	mAbs	II

Source: BioMedTracker

PRICING, MARKET POTENTIAL, NPV

In the past five years, several new drugs have been approved by the FDA for the treatment of MS, particularly for relapsing forms and active SPMS (Figure 22). These recent approvals reflect a shift toward more targeted and tolerable therapies, including oral small molecules and anti-CD20 monoclonal antibodies.

Siponimod (Mayzent), approved in 2019 and developed by Novartis (NVS; Not Rated), is an oral S1P receptor modulator indicated for active SPMS and relapsing MS. It helps reduce disease progression and relapse frequency and has an annual list price around $88,500[69]. In the same year, Diroximel fumarate (Vumerity) from Biogen (BIIB; Not Rated) was also approved for relapsing MS and active SPMS. It's a next-generation fumarate designed to reduce gastrointestinal side effects compared to its predecessor (dimethyl fumarate), with a comparable annual cost of $88,000[70].

Ozanimod (Zeposia), launched by Bristol Myers Squibb (BMY; Not Rated) in 2020, is another oral S1P receptor modulator approved for relapsing MS, including active SPMS, with annual cost of approximately $86,000[71] making it one of the more accessible new options. That same year, Ofatumumab (Kesimpta), a subcutaneous anti-CD20 monoclonal antibody developed by Novartis, was approved for relapsing MS. Designed for monthly self-administration, Kesimpta offers targeted B-cell depletion with a list price near $83,000 per year[72].

In 2021, Ponesimod (Ponvory) from Janssen (JNJ; Not Rated) entered the market as yet another S1P modulator for relapsing MS and active SPMS. Though exact pricing data is less transparent, it aligns with the class average of $84,000–$120,000/year[73]. More recently, Ublituximab (Briumvi) by TG Therapeutics (TGTX; Not Rated) received approval in 2022 for relapsing MS, offering a lower-cost intravenous anti-CD20 option at about $59,000/year—notably undercutting both Ocrevus and Kesimpta[74].

Finally, in 2024, a new subcutaneous formulation of ocrelizumab called Ocrevus Zunovo was approved. Developed by Genentech (Roche (ROG.SW; Not Rated)), it is used for both relapsing MS and primary progressive MS (PPMS). Its annual cost remains close to the IV version, typically around $65,000–$79,000[75].

None of the currently approved drugs specifically target non-active secondary progressive MS. Therefore, if intranasal foralumab is approved, it may command a premium price. We assume an annual cost of approximately $85,000. The pending patent for the use of intranasal foralumab in treating CNS indications expires in 2043, giving the product an estimated 12-year commercial life. If the company secures approval following a pivotal trial, we project US launch in 2029, followed by the EU5 in 2030. Based on a 50% market share (Figure 23), the drug could achieve approximately $1.6B in net sales in the US and $1B in the EU5, where we assume a pricing level at two-thirds of the US list price.

The combined risk-adjusted (45% probability of success) NPV for intranasal foralumab is ~$1.2B ($8/share), according to our model (Figure 24).

FINANCIALS

As of December 31, 2024, the company reported ~$3.7M in cash, cash equivalents, and investments. We estimate that the annual cash burn is approximately $21M.

[69] https://www.biopharmadive.com/news/novartis-mayzent-multiple-sclerosis-approval-secondary-progressive/551419/
[70] https://multiplesclerosisnewstoday.com/national-ms-society-objects-vumerity-list-price/
[71] https://www.fiercepharma.com/marketing/bristol-myers-squibb-s-zeposia-launches-into-crowded-multiple-sclerosis-market-amid-covid
[72] https://www.dvcstem.com/post/kesimpta-vs-ocrevus
[73] https://www.mmitnetwork.com/aishealth/spotlight-on-market-access/most-payers-expect-to-manage-new-ms-drug-ponvory-to-label-2/
[74] https://multiplesclerosisnewstoday.com/news-posts/relapsing-ms-therapy-briumvi-commercially-available-us/
[75] https://www.gene.com/stories/how-we-priced-our-breakthrough-medicine-for-multiple-sclerosis

Figure 22: Pricing of Recent Approved Drugs for MS

Drug (Brand)	Lead Company	Approval Year	Mechanism of Action	Modality	Targeted MS Type	Annual Price
Siponimod (Mayzent)	Novartis	2019	S1P receptor modulator	Oral small molecule	Active SPMS & relapsing	$88,500
Diroximel fumarate (Vumerity)	Biogen	2019	Nrf2 pathway activator (fumarate derivative)	Oral small molecule	Relapsing MS & active SPMS	$88,000
Ozanimod (Zeposia)	Bristol Myers Squibb	2020	S1P receptor modulator	Oral small molecule	Relapsing MS, active SPMS	$86,000
Ofatumumab (Kesimpta)	Novartis	2020	Anti-CD20 monoclonal antibody	Subcutaneous biologic	Relapsing MS	$83,000
Ponesimod (Ponvory)	Janssen (J&J)	2021	S1P receptor modulator	Oral small molecule	Relapsing MS, active SPMS	$85,000
Ublituximab (Briumvi)	TG Therapeutics	2022	Anti-CD20 monoclonal antibody	Intravenous biologic	Relapsing MS, active SPMS	$59,000
Ocrevus Zunovo	Genentech (Roche)	2024	Anti-CD20 monoclonal antibody	Subcutaneous biologic	Relapsing & primary progressive MS	$65,000
					Average	$79,214
					Median	$85,000

Source: BioMedTracker & Lucid Capital Markets Research

Figure 23: Market Model (US + EU5)

Multiple Sclerosis Market - US		2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E	2033E	2034E	2035E	2036E	2037E	2038E	2039E	2040E	2041E	2042E	2043E
($ in thousands except price)																				
US Population (in 000s)		343,523	345,241	346,967	348,702	350,446	352,198	353,959	355,729	357,507	359,295	361,091	362,897	364,711	366,535	368,367	370,209	372,060	373,921	375,790
% U.S. Population Growth	*0.5%*																			
Patients with na-SPMS		23,703	23,822	23,941	24,060	24,181	24,302	24,423	24,545	24,668	24,791	24,915	25,040	25,165	25,291	25,417	25,544	25,672	25,801	25,930
*% Prevalence **	*0.01%*																			
Annual Patient Treated						2,418	4,860	7,327	9,818	12,334	12,396	12,458	12,520	12,583	12,645	12,709	12,772	12,836	12,900	12,965
Market Penetration						*10%*	*20%*	*30%*	*40%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*
Annual Treatment Cost **						$85,000	$89,250	$85,000	$89,250	$93,713	$98,398	$103,318	$108,484	$113,908	$119,604	$125,584	$131,863	$138,456	$145,379	$152,648
Total US Gross sales						**$205,536**	**$433,785**	**$622,791**	**$876,266**	**$1,155,850**	**$1,219,711**	**$1,287,100**	**$1,358,212**	**$1,433,253**	**$1,512,441**	**$1,596,003**	**$1,684,182**	**$1,777,233**	**$1,875,425**	**$1,979,043**
Gross-to-Net Ratio %	*80%*																			
Total US Net Sales						**$164,429**	**$347,028**	**$498,233**	**$701,013**	**$924,680**	**$975,769**	**$1,029,680**	**$1,086,570**	**$1,146,603**	**$1,209,953**	**$1,276,802**	**$1,347,346**	**$1,421,787**	**$1,500,340**	**$1,583,234**

* Estimated prevalence of non-active SPMS is 6.9 per 100,000 people . Source: https://bmcneurol.biomedcentral.com/articles/10.1186/s12883-022-02820-0

** Current estimated drug price range for secondary progressive MS is $65,000 – $95,000 per year in the US

Source: Tiziana Life Sciences SEC filings, Lucid Capital Markets estimates

Multiple Sclerosis Market - EU5		2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E	2033E	2034E	2035E	2036E	2037E	2038E	2039E	2040E	2041E	2042E	2043E
($ in thousands except price)																				
EU5 Population (in 000s)		323,370	324,567	325,768	326,973	328,183	329,397	330,616	331,839	333,067	334,299	335,536	336,778	338,024	339,275	340,530	341,790	343,055	344,324	345,598
% EU Population Growth	*0.37%*																			
Patients with na-SPMS		22,313	22,395	22,478	22,561	22,645	22,728	22,813	22,897	22,982	23,067	23,152	23,238	23,324	23,410	23,497	23,584	23,671	23,758	23,846
*% Prevalence **	*0.01%*																			
Annual Patient Treated							2,273	4,563	6,869	9,193	11,533	11,576	11,619	11,662	11,705	11,748	11,792	11,835	11,879	11,923
Market Penetration							*10%*	*20%*	*30%*	*40%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*
Annual Treatment Cost **							$58,905	$61,850	$58,905	$61,850	$64,943	$68,190	$71,599	$75,179	$78,938	$82,885	$87,030	$91,381	$95,950	$100,748
% of EU Price / US Price	*66%*																			
Total US Gross sales							**$133,882**	**$282,192**	**$404,623**	**$568,568**	**$749,006**	**$789,367**	**$831,902**	**$876,729**	**$923,971**	**$973,759**	**$1,026,230**	**$1,081,529**	**$1,139,807**	**$1,201,225**
Gross-to-Net Ratio %	*80%*																			
Total EU5 Net Sales							**$107,105**	**$225,753**	**$323,698**	**$454,854**	**$599,205**	**$631,493**	**$665,521**	**$701,383**	**$739,177**	**$779,007**	**$820,984**	**$865,223**	**$911,846**	**$960,980**

* We assume similar prevalence in EU5 as US

*** We assume EU5 will have the list price 66% of the one in the US*

Source: Tiziana Life Sciences SEC filings, Lucid Capital Markets estimates

Figure 24: NPV Model

NPV Calculation			2024A	2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E	2033E	2034E	2035E	2036E	2037E	2038E	2039E	2040E	2041E	2042E	2043E
Total Revenue			-	-	-	-	-	$164,429	$454,133	$723,986	$1,024,711	$1,379,534	$1,574,974	$1,661,173	$1,752,091	$1,847,986	$1,949,130	$2,055,810	$2,168,330	$2,287,010	$2,412,186	$2,544,215
COGS			-	-	-	-	-	($16,443)	($45,413)	($72,399)	($102,471)	($137,953)	($157,497)	($166,117)	($175,209)	($184,799)	($194,913)	($205,581)	($216,833)	($228,701)	($241,219)	($254,421)
% of COGS		*10%*																				
Total Gross Profit			**-**	**-**	**-**	**-**	**-**	**$147,986**	**$408,720**	**$651,587**	**$922,240**	**$1,241,581**	**$1,417,476**	**$1,495,056**	**$1,576,882**	**$1,663,187**	**$1,754,217**	**$1,850,229**	**$1,951,497**	**$2,058,309**	**$2,170,967**	**$2,289,793**
R&D			($5,229)	($10,600)	($16,000)	($19,200)	($23,040)	($27,648)	($33,178)	($33,178)	($33,178)	($33,178)	($33,178)	($33,178)	($33,178)	($33,178)	($33,178)	($33,178)	($33,178)	($33,178)	($33,178)	($33,178)
SG&A			($10,565)	($12,000)	($12,000)	($12,000)	($12,000)	($73,993)	($122,616)	($130,317)	($92,224)	($124,158)	($141,748)	($149,506)	($157,688)	($166,319)	($175,422)	($185,023)	($195,150)	($205,831)	($217,097)	($228,979)
SG&A as % of Revenue								*50%*	*30%*	*20%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*
Operating Income (EBIT)			**($15,794)**	**($22,600)**	**($28,000)**	**($31,200)**	**($35,040)**	**$46,345**	**$252,926**	**$488,092**	**$796,839**	**$1,084,245**	**$1,242,551**	**$1,312,373**	**$1,386,016**	**$1,463,691**	**$1,545,617**	**$1,632,028**	**$1,723,170**	**$1,819,300**	**$1,920,693**	**$2,027,636**
Probability-adjusted EBIT	*PoS*																					
	45%																					
Total Probability-adjusted EBIT			**($15,794)**	**($22,600)**	**($28,000)**	**($31,200)**	**($35,040)**	**$20,855**	**$113,817**	**$219,642**	**$358,577**	**$487,910**	**$559,148**	**$590,568**	**$623,707**	**$658,661**	**$695,528**	**$734,413**	**$775,426**	**$818,685**	**$864,312**	**$912,436**
Tax Expense	*21%*		-	-	-	-	-	-	-	($46,125)	($75,301)	($102,461)	($117,421)	($124,019)	($130,979)	($138,319)	($146,061)	($154,227)	($162,840)	($171,924)	($181,505)	($191,612)
Free Cash Flow			($15,794)	($22,600)	($28,000)	($31,200)	($35,040)	$20,855	$113,817	$173,517	$283,276	$385,449	$441,727	$466,549	$492,729	$520,342	$549,467	$580,186	$612,587	$646,761	$682,806	$720,825
Discount rate	*15%*																					
NPV of FCF		**$1,186,498**																				
Shares Outstanding in Thousands		141,211																				
NPV of FCF per Share		**$8**																				

In millions except per share values

MANAGEMENT

Ivor Elrifi – Chief Executive Officer & Executive Director

Ivor Elrifi serves as the Chief Executive Officer and Executive Director. Mr Elrifi was formerly the global head of the Patent Group at Cooley since 2014 and before that the global head of Patents at Mintz Levin from 1999 – 2014. He has counseled companies in various key industries, including pharmaceutical, biotechnology, life sciences and medical device companies, research institutions, universities, hospitals and governments throughout the world, particularly in the US and Europe. Ivor has guided clients in developing and implementing intellectual property strategies and in the prosecution, licensing and enforcement of patents. He has extensive experience in advising clients on strategic transactional work and regularly counsels' clients with respect to investments, business development and mergers and acquisitions, including acquisition transactions involving Novartis, Eli Lilly, Biogen and Astellas.

He has received various awards throughout his career, including being named an "LMG Life Sciences: Life Science Star," and ranked nationally in Chambers USA since 2007. Elrifi earned his B.S. and Ph.D. in Biology from Queen's University and his J.D. from Osgoode Hall Law School.

Keeren Shah – Chief Operating Officer & Chief Financial Officer

Keeren Shah is a dynamic executive who currently serves as the Chief Operating Officer and Chief Financial Officer, bringing strategic vision and operational excellence to the role. In addition to her leadership here, she is also the CFO of OKYO Pharma Ltd, Accustem Sciences Limited, and Rasna Therapeutics Inc.

Ms. Shah joined the group in 2016 as Group Financial Controller, where she played a pivotal role in strengthening financial governance and operational efficiency across multiple businesses until her promotion in 2020. Earlier in her career, she spent a decade at Visa, Inc., where she was a senior leader in the finance organization. There, she led transformative finance initiatives, contributed to the success of Visa's landmark IPO, and oversaw critical FP&A and controller functions during a period of global expansion.

Ms. Shah began her career in finance with roles at Arthur Andersen and BBC Worldwide, gaining diverse industry experience and sharpening her leadership skills. She holds a BA (Hons) in Economics and is a member of the Chartered Institute of Management Accountants.

A respected leader known for her cross-sector expertise and results-driven mindset, Ms. Shah thrives at the intersection of finance, strategy, and innovation.

William Clementi, PhD – Chief Development Officer

Dr. Clementi has followed a science-driven career path since completing his NIH Training Fellowship (under John L. McNay M.D. and Thomas M. Ludden Ph.D.) Upon completing his Fellowship research in drug metabolism and vascular smooth muscle relaxation, Dr. Clementi joined the University of Texas Graduate School of Biomedical Sciences (UTGBS) faculty and the College of Pharmacy faculty in Austin, Tx, in the Departments of Medicine and Pharmacology at the Health Sciences Center in San Antonio. His primary responsibilities were interdisciplinary, and he led innovative programs in the Colleges with teaching, research, and clinical commitments. Dr. Clementi directed the Clinical Pharmacokinetic Consultation Service, providing novel computer-based drug dosing to the acute care settings at two major teaching hospitals.

Dr. Clementi continued his career in the pharmaceutical industry, joining Synthelabo and the US affiliate Lorex Pharmaceuticals, where he held the Worldwide Director of Market Development position. Lorex and Synthelabo launched three EMA and FDA-approved products (betaxolol, zolpidem, and alfuzosin).

In 1991 Dr. Clementi established a regulatory consulting company, Clementi & Associates, Ltd. (dba as Clementi Ltd). Clementi Ltd. provides regulatory and clinical consultation to small companies developing drugs, biologics, cell-based therapies, organ sustainability products and contrast media for medical imaging. Clementi Ltd. has experience with required regulatory submission standards and processes, including orphan designation, exploratory INDs, expanded access INDs, and combination drug-drug and device-drug products. Clementi Ltd also provides high-level cGMP and GCP oversight.

Dr. Clementi is a graduate of Boston University and the University of Texas and the College of Pharmacy.

RISKS

Tiziana Life Sciences is a development-stage company, and investment is subject to risk.

Clinical Trial Risk

The company is progressing on multiple clinical studies for intranasal foralumab. Early data are encouraging and warrant further clinical development. Intranasal foralumab was found to be safe and effective, without any serious adverse events. However, in the ongoing clinical trials, intranasal foralumab may not be deemed safe and effective. So far, interim safety analyses of all clinical trials conducted have not identified any significant safety concerns.

Regulatory Risk

The FDA and European regulators may require additional clinical trials for Intranasal foralumab beyond the ones Tiziana currently anticipates.

Competition Risk

Intranasal foralumab is facing competition from existing approved drugs and other drug candidates for treating MS, AD and ALS.

Financing Risk

The cash position was around $3.7M (December 2024). We estimate the company to burn approximately $21M over the next 12 months. The company needs to raise additional equity capital to support its clinical development, unless licensing deals are forged for its development-stage assets. Financing may not be available under favorable terms, or at all.

Income Statements

Tiziana Life Sciences											Elemer Piros, Ph.D. 646-350-1528 epiros@lucidcm.com
			2024A			2025E			2026E		
($ In thousands, except per share data)	**2022A**	**2023A**	**1HA**	**2HA**	**2024A**	**1HE**	**2HE**	**2025E**	**1HE**	**2HE**	**2026E**
Operating Expenses											
Research and development	**($12,955)**	**($8,113)**	($2,575)	($2,654)	**($5,229)**	($2,600)	($8,000)	**($10,600)**	($8,000)	($8,000)	**($16,000)**
Operating expenses	**($1,631)**	**($9,871)**	($3,931)	($6,634)	**($10,565)**	($6,000)	($6,000)	**($12,000)**	($6,000)	($6,000)	**($12,000)**
Loss from operations	**($14,586)**	**($17,984)**	($6,506)	($9,288)	**($15,794)**	($8,600)	($14,000)	**($22,600)**	($14,000)	($14,000)	**($28,000)**
Finance Income	($7)	$1,144	$112	$702	**$814**	$407	$407	**$814**	$407	$407	**$814**
FV Loss on Investment	($869)	($402)	($1,585)	($181)	**($1,766)**	-	-	-	-	-	-
Other Income	$65	-	-	-	-	-	-	-	-	-	-
Total Other Income	**($811)**	**$742**	($1,473)	$521	**($952)**	$407	$407	**$814**	$407	$407	**$814**
Income Tax / Credit	**-**	**($449)**	$3,326	$1,557	**$4,883**	-	-	-	-	-	-
Net (loss) income	**($15,397)**	**($17,691)**	($4,653)	($7,210)	**($11,863)**	($8,193)	($13,593)	**($21,786)**	($13,593)	($13,593)	**($27,186)**
Weighted average number of shares outstanding	**101,526**	**102,471**	103,098	106,672	**106,672**	113,135	121,529	**121,529**	132,674	139,155	**139,155**
Net loss attributable to common stockholders per share	**($0.15)**	**($0.17)**	($0.05)	($0.07)	**($0.11)**	($0.07)	($0.11)	**($0.18)**	($0.10)	($0.10)	($0.20)

Source: Tiziana Life Sciences SEC filings, Lucid Capital Markets estimates

Risks for: Tiziana Life Sciences Ltd (TLSA)

Tiziana Life Sciences is a development-stage company, and investment is subject to risk.

Clinical Trial Risk

The company is progressing on multiple clinical studies for intranasal foralumab. Early data are encouraging and warrant further clinical development. Intranasal foralumab was found to be safe and effective, without any serious adverse events. However, in the ongoing clinical trials, intranasal foralumab may not be deemed safe and effective. So far, interim safety analyses of all clinical trials conducted have not identified any significant safety concerns.

Regulatory Risk

The FDA and European regulators may require additional clinical trials for Intranasal foralumab beyond the ones Tiziana currently anticipates.

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Intranasal foralumab is facing competition from existing approved drugs and other drug candidates for treating MS, AD and ALS.

Financing Risk

The cash position was around $3.7M (December 2024). We estimate the company to burn approximately $21M over the next 12 months. The company needs to raise additional equity capital to support its clinical development, unless licensing deals are forged for its development-stage assets. Financing may not be available under favorable terms, or at all.

Valuation for: Tiziana Life Sciences Ltd (TLSA)

We arrive at our 12-month price target of $8 per share by assessing the after-tax, risk-adjusted NPV of potential future cash flows from foralumab in non-active SPMS. The probability-adjusted (45%), fully taxed (21%) NPV at a 15% discount rate of potential cash flows until 2043 is approximately $1.2B, equivalent to $8 per share, corresponding to our 12-month price target. Potential factors that could prevent shares from reaching our price target include the failure of foralumab to demonstrate significant efficacy benefits or being deemed unsafe, leading to the discontinuation of clinical programs and commercial launch. In addition, the company may not be able to raise additional funds to complete development.

Company Description for: Tiziana Life Sciences Ltd (TLSA)

Tiziana Life Sciences is a clinical-stage biopharmaceutical company developing breakthrough therapies using transformational drug delivery technologies to enable alternative routes of immunotherapy. Tiziana's innovative nasal approach has the potential to provide an improvement in efficacy as well as safety and tolerability compared to intravenous (IV) delivery. Tiziana's lead candidate, intranasal foralumab, which is the only fully human anti-CD3 mAb currently in clinical development, has demonstrated a favorable safety profile and clinical response in patients in studies to date. Tiziana's technology for alternative routes of immunotherapy has been patented with several applications pending and is expected to allow for broad pipeline applications.

Appendix

Important Legal Disclaimers

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Rating distribution (as of) July 21, 2025	Investment Banking Relationships
Buy: 81.0%	Buy: 84.6%
Neutral: 19.0%	Neutral: 15.4%
Sell: 0.0%	Sell: 0.0%
Not Rated: 0.0%	Not Rated: 0.0%

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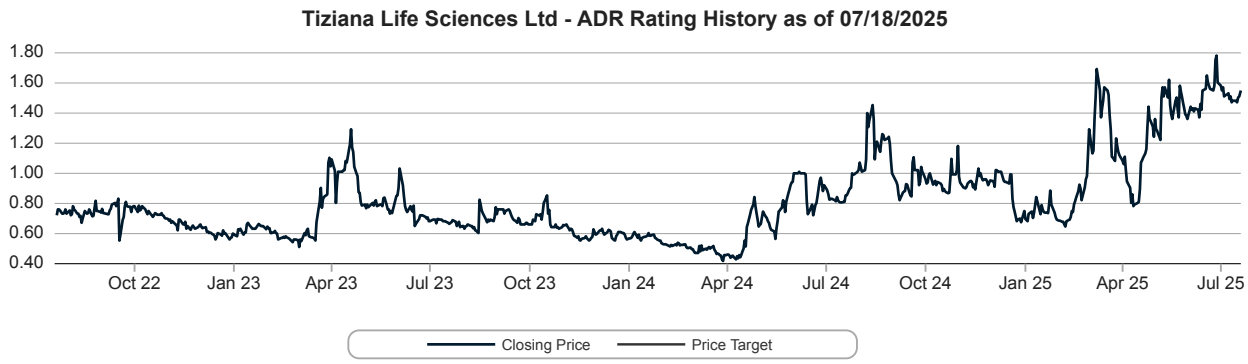
Tiziana Life Sciences Ltd - ADR Rating History as of 07/18/2025
1.80
1.60
1.40
1.20
1.00
0.80
0.60
0.40
Oct 22
Jan 23
Apr 23
Jul 23
Oct 23
Jan 24
Apr 24
Jul 24
Oct 24
Jan 25
Apr 25
Jul 25
Closing Price
Price Target