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THE CNS RENAISSANCE
INNOVATIONS ARE RESHAPING NEUROLOGICAL THERAPIES

THEMES

As one of the largest issuer-sponsored research firms, we are known for our bottom-up work on individual stocks. However, our thinking does not stop at the company level. Through our regular dialogue with management teams and investors, we consider the broad themes related to the companies we follow. Edison themes aims to identify the big issues likely to shape company strategy and portfolios in the years ahead.

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The CNS renaissance

Innovations are reshaping neurological therapies

Central nervous system (CNS) conditions are among the most significant unmet medical needs globally, with neurological conditions now one of the leading causes of disabilities, and having an impact on over 3.4 billion people worldwide. After decades of limited progress, the CNS field is experiencing a renaissance marked by novel technological advances that are overcoming barriers to effective drug development. Sophisticated blood-brain barrier crossing technologies are finally solving the fundamental delivery challenge, while AI-powered platforms are making unprecedented advances in drug discovery and biomarker identification. Most critically, the development of blood-based biomarkers is enabling early diagnosis and precision patient monitoring, addressing key issues that have historically limited CNS therapeutic success rates.

Disease-modifying therapies validate the shift

Recent landmark approvals demonstrate the shift from symptomatic treatments to genuine disease-modification. Biogen's Leqembi and Eli Lilly's Kisunla are the first disease-modifying Alzheimer's therapies in two decades, while Bristol Myers Squibb's Cobenfy is the first new schizophrenia mechanism in 35 years. These approvals establish regulatory precedents and show that disease modification is achievable in previously intractable CNS conditions, creating pathways for next-generation therapies targeting neuroinflammation, tau pathology and synaptic dysfunction.

Big pharma's strategic re-engagement

Major pharmaceutical companies are returning to neuroscience with over $50bn of M&A activity across the past couple of years, including Johnson & Johnson's $14.6bn Intra-Cellular acquisition and Bristol Myers Squibb's $14.0bn Karuna purchase. Novartis's partnership with Arrowhead Pharmaceuticals exemplifies strategic licensing, with $200m upfront and $2.0bn in potential milestones for alpha-synuclein RNA therapy. This re-engagement reflects massive unmet need and an impending patent cliff threatening $200bn in annual sales through 2030.

Investment landscape transformation

CNS start-ups attracted venture capital of $1.7bn in 2024, an 80% y-o-y increase, making neuroscience the third-largest specialty in venture funding. Investment opportunities span dedicated neuroscience exchange-traded funds (ETFs), established pharmaceutical CNS franchises, mid-cap specialists and small-cap biotechnology platform companies. Key themes include blood-brain barrier technologies, AI-driven discovery, psychedelic therapeutics, cell and gene therapies and precision neuroinflammation approaches.

22 September 2025

Edison themes

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Companies mentioned in this report:

AbbVie (NYSE: ABBV)
AC Immune (NASDAQ: ACIU)
Actinogen Medical (ASX: ACW)*
Alnylam Pharmaceuticals (NASDAQ: ALNY)
Alzinova (OMX: ALZ)
Anavex Life Sciences (NASDAQ: AVXL)
Annovis Bio (NYSE: ANVS)
Arrowhead Pharmaceuticals (NASDAQ: ARWR
AstraZeneca (LSE: AZN)
ATAI Life Sciences (NASDAQ: ATAI)
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uniQure (NASDAQ: QURE)
Voyager Therapeutics (NASDAQ: VYGR)
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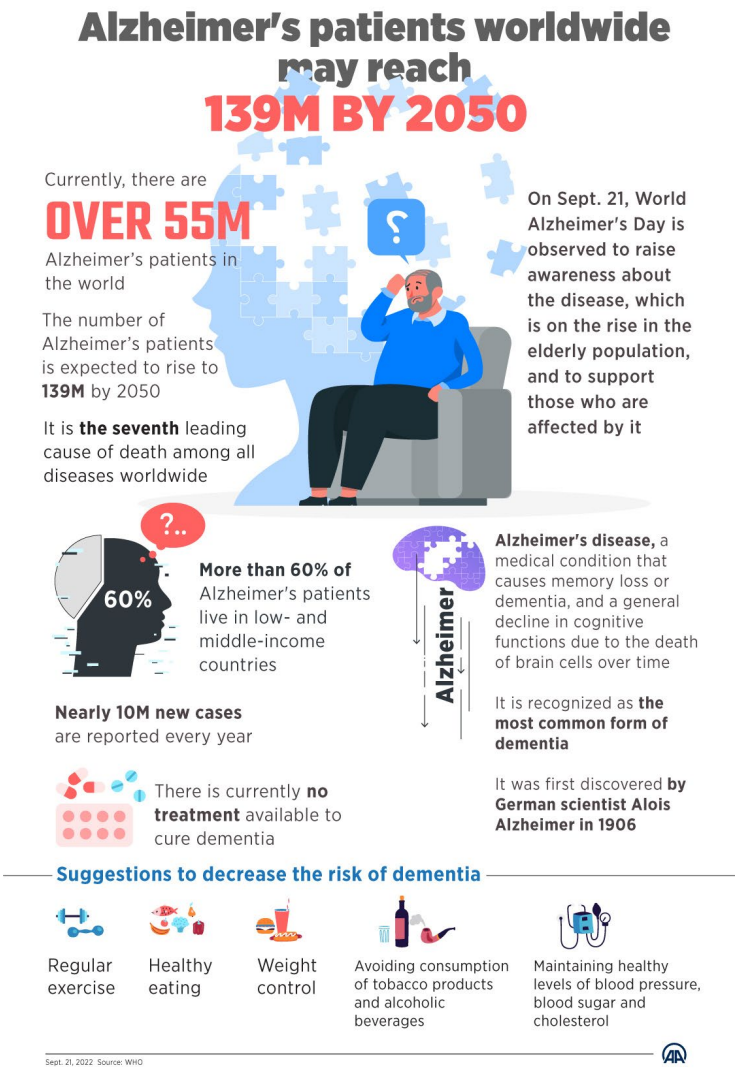
The great unmet need

Disease burden and demographics

Exhibit 1: 55 million people globally with Alzheimer's disease

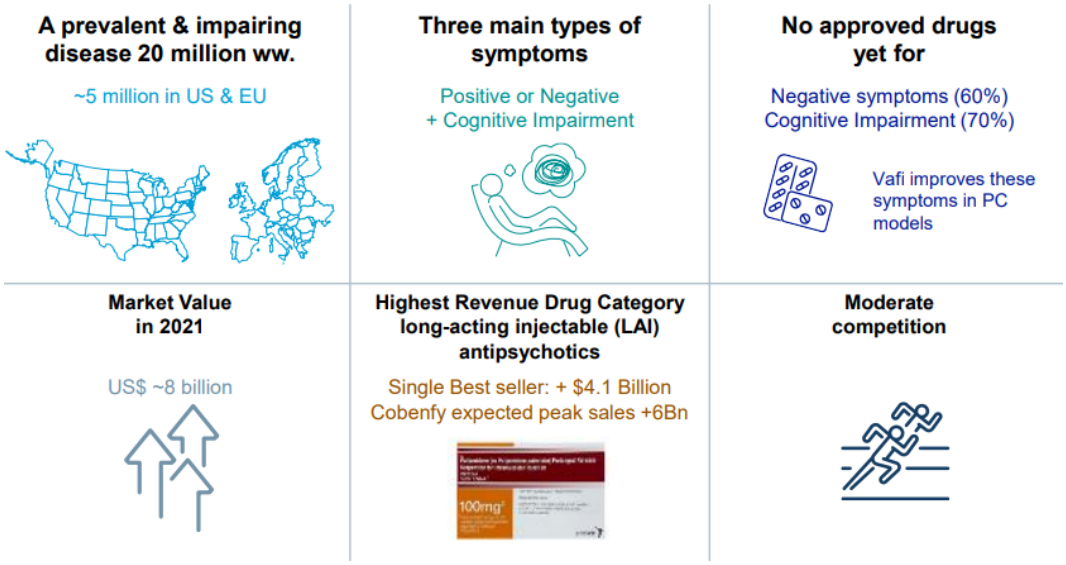


Source: World Health Organization

The following statistics, relating to both neurodegenerative and neuropsychiatric conditions, demonstrate the magnitude of the challenge:

- **Alzheimer's disease** affects over 55 million people globally, projected to reach 78 million by 2030.
- **Parkinson's disease** affects more than 10 million people worldwide according to the Parkinson's Foundation, making it the second most prevalent neurodegenerative condition.
- **Depression:** 21 million adults (Forbes Health) in the US suffer from major depressive episodes.
- **Anxiety conditions** affect over 50 million (Forbes Health) people in the US.
- **Schizophrenia** affects four million people in the US (Institute for Clinical and Economic Review), with treatment-resistant schizophrenia (TRS) representing nearly half of all cases.

Exhibit 2: Overview of the schizophrenia market



Source: Oryzon Genomics Investor Presentation, January 2025

The economic burden is equally overwhelming, with the annual cost of neurodegenerative and neuropsychiatric conditions estimated, creating an estimated economic burden of $800bn pa in the US alone, accounting for wider societal costs, such as reduced work capacity for patients and caregivers.

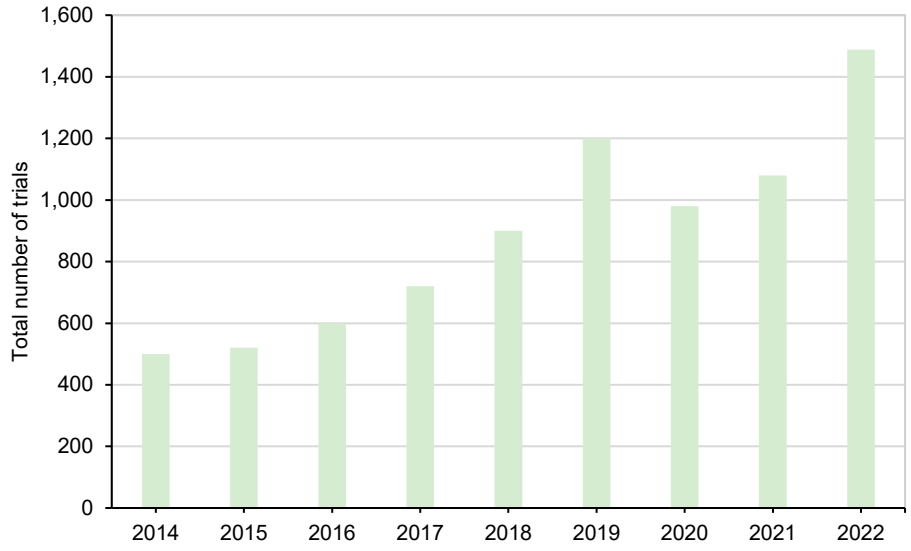
Historical challenges in CNS drug development

The complexity of the CNS has historically made it one of the most challenging therapeutic areas for drug development. The brain comprises c 86bn neurons forming quadrillions of connections, creating an intricate network that researchers are still working to understand. We discuss below several factors that have contributed to the low success rates in CNS drug development.

High clinical trial failure rates: a landmark 2014 study by Tufts Center for the Study of Drug Development found that CNS compounds had a success rate of only 6.2% from investigational new drug (IND) application to approval. This corresponds to less than half the success rate for non-CNS drugs, which was reported at 13.3%, and more recent research from GlobalData suggests that these challenges are not only persisting, but intensifying. Between 2014 and 2022, the number of halted CNS trials surged dramatically, peaking at 1,488 terminations, suspensions and withdrawals in 2022. Phase II trials have been particularly affected, with terminations rising from 204 in 2014 to 650 in 2022, more than tripling in less than a decade. Even Phase III trials face frequent halts, with 103 terminations recorded in 2022.

The primary cause of these failures is recruitment difficulties, accounting for over half (50.7%) of trial terminations (where data were available). CNS clinical studies often require participants with specific disease stages or rare conditions, making recruitment both slow and expensive. Financial pressures represent the second most common cause of trial halts (15.2%), while lack of efficacy accounts for 10.6% of failures, highlighting the persistent difficulty of translating preclinical promise into meaningful therapeutic benefits for patients. Clinical development timelines continue to be c 18% longer for CNS drugs, compared to other therapeutic areas, reflecting the inherent complexity of demonstrating efficacy in neurological conditions.

Exhibit 3: CNS clinical trials suspended, terminated or withdrawn, 2014–22



Source: Clinical Trials database

Incomplete understanding of disease mechanisms: the pathophysiology of many CNS conditions remains poorly understood, making it difficult to identify appropriate therapeutic targets. This has been particularly evident in neurodegenerative diseases, where multiple interconnected pathways are believed to contribute to disease progression. Unlike cardiovascular diseases or certain cancers where clear mechanistic pathways have been elucidated, CNS conditions often involve complex interactions between genetic predisposition, environmental factors, protein aggregation, neuroinflammation and synaptic dysfunction. This complexity makes it challenging to determine which pathway (or pathways) to target.

Lack of reliable biomarkers: unlike other therapeutic areas, oncology in particular, CNS conditions have historically lacked reliable biomarkers for early detection, patient stratification and treatment monitoring. This has made clinical trial design challenging, contributing to high failure rates. In oncology, biomarkers like HER2 expression or EGFR mutations guide treatment selection and are used to monitor responses. In contrast, CNS conditions have traditionally relied on subjective clinical assessments and cognitive testing, making it difficult to detect early therapeutic effects or identify patients most likely to respond to specific treatments.

Limited animal model predictivity: preclinical animal models have proved largely unreliable for predicting human clinical outcomes in CNS conditions, leading to numerous late-stage clinical trial failures, despite promising preclinical results. The fundamental differences between human and animal brain architectures, particularly in higher-order cognitive functions, mean that therapeutic effects observed in animal models often fail to translate to humans. This translational gap has been particularly problematic in Alzheimer's disease research, where numerous compounds showing promise in mouse models have failed in human studies.

This high attrition rate is particularly concerning given the limited therapeutic options available for many CNS conditions. Currently, only 2% of marketed therapies target CNS complaints outside the major areas of pain, neurodegenerative and neuropsychiatric conditions, with some niche conditions like nerve injury having highly limited treatment options.

The blood-brain barrier challenge

Perhaps the most significant technical challenge in CNS drug development is the blood-brain barrier (BBB), the brain's highly selective protective mechanism that prevents most therapeutic modalities from reaching their intended targets.

The BBB consists of tightly connected endothelial cells, pericytes and astrocytes that form an effective barrier against pathogens and toxins. However, this same protective mechanism severely limits drug delivery to the brain:

- **Biologic drugs** including many peptides, proteins and antibodies cannot cross the BBB, unless carefully optimised and formulated to do so through their delivery mechanisms. We note that some smaller peptides, like those developed by companies such as Herantis Pharma, can achieve brain penetration, though only through significantly optimised properties.
- **Small-molecule drugs** can only penetrate the barrier if optimised to do so (considering a range of medicinal chemistry parameters). These are typically very small molecules, such as some antidepressants, anxiolytics and antipsychotics.

We note that while there are multiple CNS treatments that can cross the BBB, a significant portion of these tend to be symptomatic CNS treatments, highlighting that the fundamental challenge lies not solely in drug delivery, but also in our understanding of disease biology. The lack of disease-modifying therapies available stems primarily from incomplete knowledge of what targets to pursue among complex disease biological pathways. The BBB presents an additional hurdle for many potentially disease-modifying biologics and advanced small molecule therapeutics that aim to address underlying pathology, rather than just symptoms.

Exhibit 4: Roche explainer on the BBB (click to play video)

Source: Roche

This combination of limited mechanistic understanding and delivery challenges has meant that most available CNS treatments that have been developed focused on symptomatic relief through better-understood neurotransmitter pathways. The BBB effectively excludes many potentially therapeutic proteins, antibodies, gene therapies and some small molecules that have shown promise in other therapeutic areas, while an incomplete grasp of disease mechanisms limits capabilities in identifying the right targets for true disease-modification. Until recently, these twin challenges seemed insurmountable, contributing to pharmaceutical companies' exodus from CNS research during the 2010s.

Technological breakthroughs enabling the renaissance

The current CNS renaissance is underpinned by several revolutionary technological advances that are overcoming historical barriers to the effective development of novel and innovative treatment options.

Blood-brain barrier crossing technologies

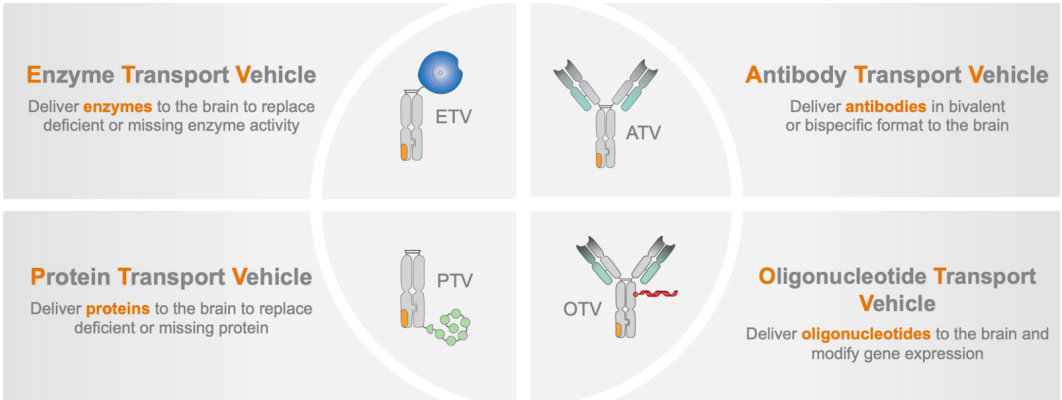
The development of sophisticated drug delivery systems represents perhaps the most significant breakthrough in CNS therapeutics. Several innovative approaches are now enabling therapies to cross the BBB effectively, which we discuss in further detail below.

Transcytosis-enabling modules (TEMs)

A number of platforms utilise natural biological transport mechanisms to ferry therapeutic cargo across the BBB:

- **Denali Therapeutics' transport vehicle (TV) platform** uses engineered Fc domains that bind to transferrin receptors, demonstrating 10–30x greater brain exposure for antibodies and enzymes, and over 1,000x greater exposure for oligonucleotides.
- **Aliada Therapeutics' Modular Delivery (MODEL) platform** (co-founded by Johnson & Johnson, and subsequently acquired by AbbVie) targets transferrin and CD98 receptors.
- **BioArctic's BrainTransporter technology** has shown up to 70x greater brain exposure of amyloid beta antibodies.
- **Roche's Brainshuttle technology** combines an amyloid beta-binding antibody with a transferrin receptor (TfR1) shuttle module. The company's investigational trontinemab, currently slated to start Phase III trials (TRONTIER 1 and 2) in H225, achieved amyloid reduction below the positivity threshold after 28 weeks of treatment in 91% of participants in the 3.6mg/kg cohort in the ongoing Phase Ib/IIa Brainshuttle AD study, demonstrating the potential of high CNS exposure at low doses for rapid amyloid clearance.

Exhibit 5: Denali's transport vehicle technologies



Source: Denali Therapeutics

Focused ultrasound

Focused ultrasound (FUS) is a non-invasive technology that temporarily disrupts the BBB using targeted ultrasound waves combined with microbubbles, creating therapeutic windows of up to four hours. FUS has demonstrated the ability to enable large therapeutic molecules to cross the BBB, including proteins and antibodies that are normally too large to penetrate the brain's protective barrier naturally.

Viral vector technology

Adeno-associated viruses (AAVs) can naturally breach the BBB to deliver genetic material directly to tissues within the brain. Novartis's Zolgensma, approved in 2019 for spinal muscular atrophy, showed the potential of systemically delivered AAV gene therapy. Companies like Voyager Therapeutics and uniQure are advancing AAV-based programmes for neurodegenerative diseases.

Nanotherapeutics

Nanoparticle-based delivery systems, including lipid nanoparticles and polymeric nanoparticles, can be engineered to cross the BBB through receptor-mediated transcytosis. Leading companies such as Alnylam Pharmaceuticals and Ionis Pharmaceuticals are leveraging these technologies for neurological applications.

AI integration in drug discovery

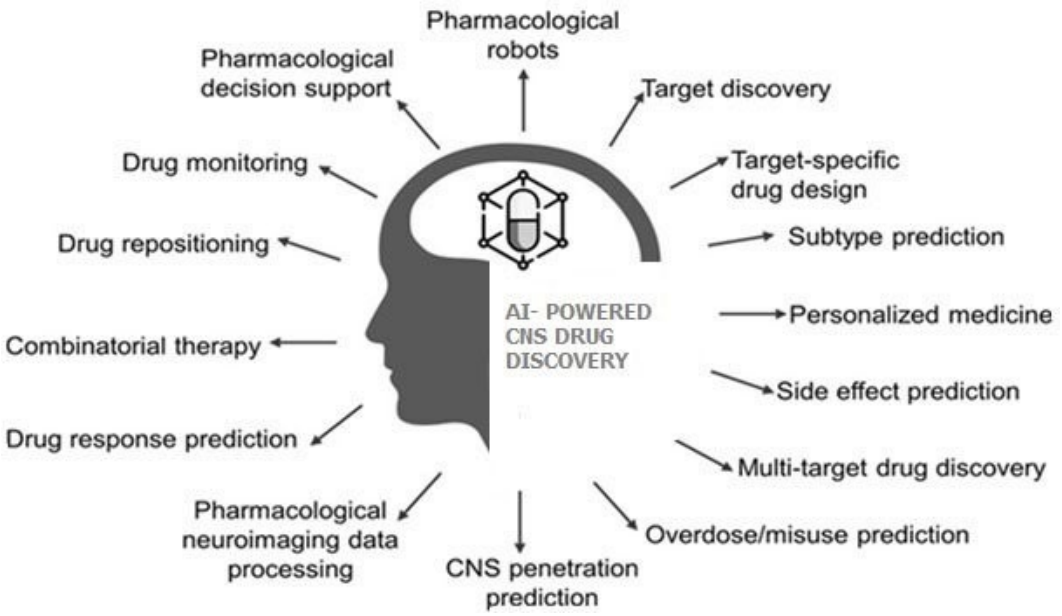
Ai and machine learning approaches are facilitating major breakthroughs in CNS drug development by enabling more precise target identification, patient stratification and treatment monitoring.

The FDA has approved over 1,000 AI devices since the mid-1990s, with neurology ranking third in approvals (behind radiology and cardiovascular applications). Half of the 42 approved neurological AI devices have been approved in just the past two years, highlighting the acceleration in AI adoption. Notably, the vast majority of these are 'locked' AI systems that operate with fixed algorithms and do not adapt or learn from new data once deployed, reflecting current regulatory frameworks that prioritise predictability and safety. Companies like IXICO are at the forefront of this transformation, with its proprietary AI-driven IXI Platform processing data from global neurological trials and precisely measuring key imaging biomarkers to help advance treatment development.

In brief, AI applications in neuroscience include:

- advanced brain imaging analysis and pattern recognition,
- biomarker discovery and validation,
- drug-target interaction prediction, and
- clinical trial optimisation.

Exhibit 6: AI integration in CNS treatments



Source: Vatansever et al. (2020). Medicinal Research Reviews. 41. 1427–1473. 10.1002/med.21764.

Blood-based biomarker revolution

The development of blood-based biomarkers represents a paradigm shift from invasive cerebrospinal fluid sampling to accessible, cost-effective diagnostic tools. We discuss some key examples below.

- **Alzheimer's disease biomarkers:** robust blood assays for amyloid and tau markers enable early detection and treatment monitoring.
- **Neurofilament light chain (NfL):** a valuable biomarker for neuronal injury across multiple conditions, including stroke, Parkinson's disease and multiple sclerosis.
- **Exosome miRNAs:** brain-derived exosomes can cross the BBB and provide insights into CNS pathology through blood analyses.

Novel therapeutic approaches and neuroinflammation

The growing recognition of the role of neuroinflammation in CNS conditions is opening new therapeutic avenues, beyond traditional approaches.

Neuroinflammation as a therapeutic target

Research increasingly demonstrates that neuroinflammation plays a central role in multiple CNS conditions, representing a pathway that could be therapeutically targeted across different conditions.

Alzheimer's disease: microglial activation and inflammatory cascades contribute to disease progression through the release of pro-inflammatory cytokines such as interleukin-1β and tumour necrosis factor-α. These inflammatory mediators exacerbate amyloid plaque formation and tau pathology, creating a self-perpetuating cycle of neurodegeneration. Activated microglia also impair the brain's ability to clear toxic protein aggregates, further accelerating disease progression.

Parkinson's disease: neuroinflammation accelerates dopaminergic neuron loss in the substantia nigra through multiple mechanisms. Alpha-synuclein aggregates trigger microglial activation, leading to the release of reactive oxygen species and inflammatory mediators that damage healthy neurons. This inflammatory response spreads beyond the initial site of pathology, contributing to the progressive nature of the disease.

Multiple sclerosis: inflammatory demyelination has long been recognised as the primary disease mechanism, driven by autoreactive T-cells that breach the BBB and attack myelin sheaths. This inflammatory assault triggers complement activation and antibody-mediated damage, leading to axonal loss and progressive disability. The inflammatory environment also impairs remyelination processes, preventing natural repair mechanisms.

Depression: inflammatory cytokines contribute to treatment resistance by disrupting neurotransmitter synthesis and signalling pathways. Elevated levels of interleukin-6, C-reactive protein and other inflammatory markers are consistently observed in treatment-resistant depression (TRD). These inflammatory mediators interfere with serotonin metabolism and reduce neuroplasticity, potentially explaining why traditional antidepressants often fail in patients with high inflammatory burden.

This role of neuroinflammation across diverse CNS conditions suggests that anti-inflammatory approaches could provide broad therapeutic benefits, potentially addressing multiple pathways simultaneously, rather than targeting individual disease-specific mechanisms.

Brain-penetrating small molecules

Unlike large biologics that often require complex delivery systems, small molecules can be carefully designed and optimised to cross the BBB, while targeting inflammatory pathways. This represents a fundamentally different approach to historical CNS drug development efforts, by leveraging the natural properties of smaller molecular structures to overcome the barrier that has previously limited such therapeutic options. We discuss below some established examples and emerging approaches.

JAK inhibitors: these small molecules can cross the BBB and modulate inflammatory signalling pathways directly within the CNS. By inhibiting Janus kinases, these compounds aim to reduce the production of pro-inflammatory cytokines that contribute to neurodegeneration and neuropsychiatric symptoms.

Novel anti-inflammatory compounds: companies are developing brain-penetrant inhibitors of specific inflammatory targets such as NLRP3 inflammasome, complement cascade components and microglial activation pathways.

Retinoid acid receptor (RAR) modulators: companies like Nevrargenics are developing innovative small molecule compounds based on RAR targeting to selectively control neuroinflammatory, neuroprotective and neuroplasticity pathways. Nevrargenics' lead compound NVG0645 (Ellorarxine) has demonstrated exceptional CNS exposure in preclinical studies and represents a multi-modal approach targeting the 'three Ns': neuroprotection, neuroplasticity and neurorepair.

Selective enzyme inhibitors: brain-penetrant compounds targeting specific enzymes involved in neuroinflammation, such as phosphodiesterase inhibitors and kinase modulators designed for optimal CNS penetration.

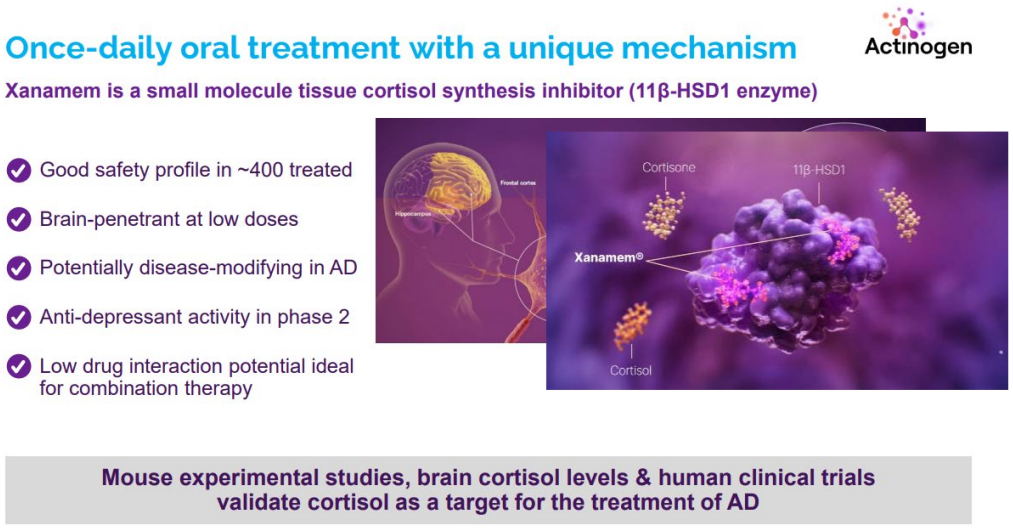
Considerations for CNS penetration and knock-on benefits

Modern medicinal chemistry approaches focus on optimising molecular properties for BBB crossing while maintaining target selectivity, considering molecular weight, lipophilicity, polar surface area and efflux pump avoidance. This approach offers several advantages:

- **Oral administration versus injectable biologics:** patients can take medications at home rather than requiring clinical visits for infusions, dramatically improving convenience and compliance, while reducing the burden on healthcare systems.
- **Lower manufacturing costs:** small molecule synthesis is typically less expensive and more scalable than the production of biologics, potentially enabling broader access to effective CNS treatments.
- **Broader patient accessibility:** oral formulations eliminate the need for specialised infusion facilities and trained healthcare providers, making treatments accessible in diverse healthcare settings, including rural and resource-limited environments.
- **Flexibility for combination with existing therapies:** small molecules can be readily combined with other small molecules or biologics without the formulation and administration challenges that can complicate biologic-biologic combinations. This enables multi-target approaches that may be necessary for complex CNS conditions.
- **Rapid onset and offset:** unlike biologics with extended half-lives, small molecules typically allow for more precise dosing control and easier discontinuation, should patients be presented with adverse side effects.
- **Potential for personalised dosing:** the pharmacokinetic properties of small molecules often enable dose adjustments based on individual patient factors, therapeutic response or genetic variations in drug metabolism. (We note that this benefit may also apply to some biologics.)

The combination of improved understanding of neuroinflammatory pathways with advanced medicinal chemistry techniques is enabling the development of brain-penetrant small molecules that aim to effectively address previously inaccessible targets, offering new hope for conditions where traditional CNS therapeutic approaches have shown limited sustained benefits.

Exhibit 7: Actinogen's Xanamem oral treatment for AD



Source: Actinogen investor presentation, July 2025

Novel therapeutic modalities

Cell and gene therapy

Advanced biological approaches are emerging as some of the most promising technologies for targeting genetic and cellular mechanisms of neurodegeneration, with the CNS representing the second-largest growth area for cell and gene therapies after oncology. GlobalData predicts explosive growth in this sector, with sales projected to soar from $2.3bn in 2024 to $12.6bn by 2030, representing a compound annual growth rate of 32.8%.

The field of gene therapy has witnessed remarkable progress and breakthroughs in addressing previously untreatable genetic neurological conditions. We discuss some examples below:

- **Spinal muscular atrophy:** Novartis's Zolgensma represents a paradigm shift, offering a one-time gene replacement therapy that has transformed outcomes for patients with this devastating condition. The treatment delivers a functional copy of the SMN1 gene using an AAV vector, demonstrating the potential for curative approaches in genetic diseases.
- **Inherited forms of blindness:** Luxturna (voretigene neparvovec) has proven that gene therapy can restore vision in patients with RPE65 mutation-associated retinal dystrophy, providing a template for addressing other inherited CNS conditions.
- **Huntington's disease:** multiple gene therapy approaches are in development, including antisense oligonucleotides designed to reduce huntingtin protein production and newer approaches targeting the somatic expansion mechanisms that drive disease progression.

The field of cell replacement therapy is experiencing renewed momentum, in particular strategies for conditions involving specific cell populations:

- **Parkinson's disease:** companies like BlueRock Therapeutics are advancing stem cell-derived dopaminergic neuron replacements into Phase III trials. These allogeneic therapies use human

pluripotent stem cells differentiated into dopaminergic neuron precursors, which are then implanted into the brain where they develop into mature dopamine neurons.

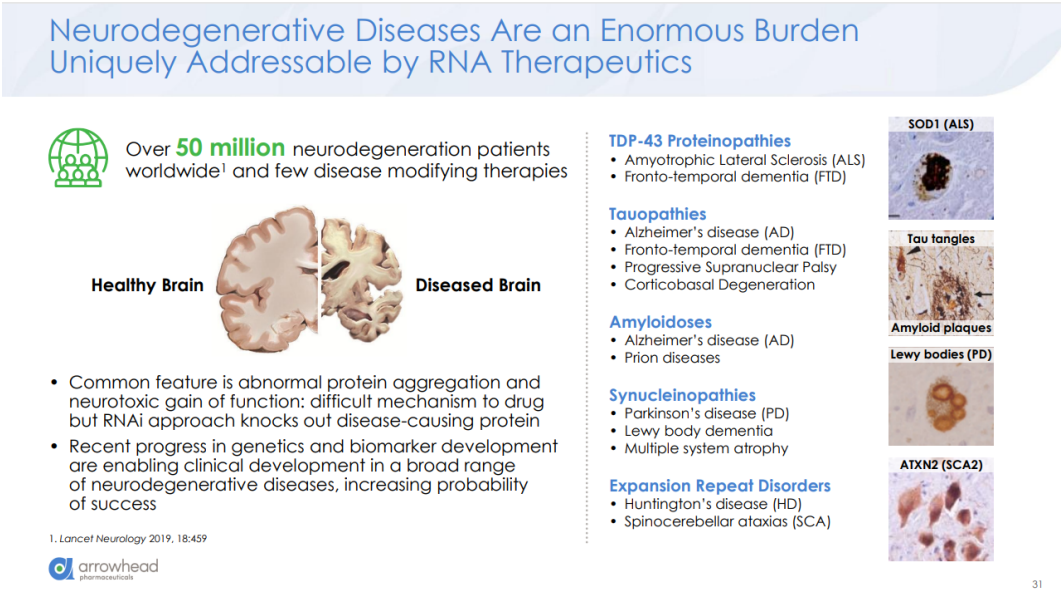
- **Epilepsy:** Neurona Therapeutics is developing cell therapies designed to replace damaged or dysfunctional neurons that normally secrete the inhibitory neurotransmitter GABA. In recent Phase I studies, patients receiving the therapy experienced long-lasting reductions in seizures, and the company is planning pivotal studies in the second half of 2025.
- **Stroke and traumatic brain injury:** emerging cell therapy approaches are exploring the potential to replace damaged neurons and support tissue repair following acute CNS injuries.

Antisense oligonucleotide and RNA interference (RNAi) therapies offer advantages in targeting previously 'undruggable' proteins and genetic mechanisms. We discuss some examples below:

- **Alpha-synuclein targeting for Parkinson's disease:** the September 2025 licensing agreement between Novartis and Arrowhead Pharmaceuticals for ARO-SNCA represents a major validation of RNAi approaches for neurodegenerative diseases. ARO-SNCA utilises Arrowhead's proprietary Targeted RNAi Molecule (TRiM) platform for subcutaneous administration with delivery to the CNS, designed to target the gene encoding alpha-synuclein protein. The platform has demonstrated impressive preclinical results showing distribution to deep brain regions after subcutaneous administration, potentially representing an important leap forward for targeting CNS-associated genes that have been historically difficult to address.
- **Genetic forms of amyotrophic lateral sclerosis (ALS):** multiple antisense programmes are targeting specific mutations, including treatments for SOD1 and C9orf72 mutations that cause familial forms of the disease.
- **Huntington's disease:** beyond traditional approaches to reduce huntingtin protein, newer strategies target the somatic expansion mechanisms that drive disease progression, potentially addressing the root cause of the condition.
- **Rare genetic epilepsies:** antisense approaches are being developed for conditions like Dravet syndrome and other genetic epilepsies where traditional drug approaches have limited efficacy.

The recent Arrowhead-Novartis partnership, with potential milestone payments up to $2.0bn, demonstrates the significant investment big pharma is making in RNA-based approaches to CNS conditions, particularly for conditions where conventional small molecules have failed to achieve meaningful disease-modification.

Exhibit 8: Arrowhead's RNAi therapeutics



Source: Arrowhead

The convergence of improved delivery technologies, better understanding of disease mechanisms and supportive regulatory frameworks is creating unprecedented opportunities for these advanced therapeutic modalities. The recent success of systemically delivered gene therapies like Zolgensma demonstrates that effective CNS delivery is achievable, while the growing pipeline of cell and gene therapies suggests this field will be a major driver of innovation in CNS therapeutics over the coming decade.

Another promising development in advanced approaches for CNS conditions is the increasing use of immunotherapy. For example, Alzinova is looking to address Alzheimer's disease through protein-modification and immunotherapy-based solutions. Lead candidate ALZ-101 combines AβCC Peptide Technology with immunotherapy by aiming to stop Aβ42 plaque build-up on synapses, to thereby prevent the neurone loss responsible for the symptoms of AD.

Psychedelics and neuroplastogens

The clinical comeback of psychedelics represents a significant shift in psychiatric treatment approaches, enabled by an evolving regulatory landscape that increasingly supports such programmes, particularly when combined with psychological interventions such as cognitive behavioural therapy. Neuroplastogens are compounds that promote structural and functional neural plasticity by stimulating neurite growth, dendritic branching and synaptogenesis – processes that can help restore healthy neural circuits in conditions characterised by synaptic dysfunction and neuronal atrophy.

Psilocybin: multiple Phase III trials ongoing for TRD, with mechanisms involving serotonin 2A receptor activation and promotion of neuroplasticity. These trials incorporate structured psychotherapy sessions alongside drug administration, recognising that the therapeutic benefit emerges from the combination of pharmacological and psychological interventions.

MDMA: advanced development for post-traumatic stress disorder, with regulatory challenges being addressed following recent FDA advisory committee discussion outcomes. Treatment protocols involve MDMA-assisted psychotherapy sessions conducted by trained therapists, emphasising the critical role of the therapeutic setting and psychological support.

LSD: MindMed's MM120, in Phase III trials for generalised anxiety, represents one of the first clinical developments of LSD in decades. The programme focuses on controlled, supervised administration in clinical settings with appropriate psychological support frameworks.

Ketamine: approved formulations available with expanded indications in development, demonstrating rapid antidepressant effects through NMDA receptor antagonism. Clinical protocols increasingly incorporate psychotherapeutic elements to maximise and sustain therapeutic benefits.

The regulatory landscape has evolved significantly to accommodate these novel approaches. The FDA's Breakthrough Therapy designation for psilocybin therapy and the establishment of specialised regulatory pathways reflect growing recognition of the potential therapeutic value when these compounds are administered in controlled clinical settings with appropriate psychological support. The emphasis on combination therapy, which integrates pharmacological intervention with structured psychotherapy, is a departure from traditional pharmaceutical development and highlights the importance of the therapeutic context in achieving optimal outcomes.

The developments mentioned above are reflected in the neuropsychiatric pipeline, which has expanded beyond traditional neurotransmitter approaches:

- Psychedelic compounds:
  - COMP360 (Compass Pathways) – synthetic psilocybin for TRD.
  - CYB003 (Cybin) – deuterated psilocybin in Phase III for major depression.
  - MM120 (MindMed) – LSD derivative for generalised anxiety condition.
- Neuroplastogen development:

- Next-generation compounds providing psychedelic-like benefits without hallucinogenic effects.
- GABA and glutamate system modulators for rapid antidepressant effects.

Exhibit 9: Overview of Phase III studies of psilocybin and MDMA

	Study Description (Sponsor)	Indication	Treatment Amount	Multiple Treatments (Yes/No)
Psilocybin	Psilocybin-assisted therapy in treatment-resistant depression (University of North Carolina, Chapel Hill)	Treatment-resistant depression	25 mg	Yes
	Efficacy, safety, and tolerability of two administrations of COMP360* in participants with TRD (Compass Pathways)	Treatment-resistant depression	1, 10, or 25 mg	Yes
	Efficacy, safety, and tolerability of COMP360* in participants with TRD (Compass Pathways)	Treatment-resistant depression	25 mg	No
	Psilocybin for major depressive disorder (Usona Institute)	Major Depressive Disorder	5 or 25 mg	No
	Frontline clinician psilocybin study (University of Washington)	Depression and Burnout	25 mg	No
	Psilocybin therapy in advanced cancer (NYU Langone Health)	Anxiety, Depression, and Existential Distress	25 mg	No
MDMA	MDMA-assisted brief cognitive-behavioral conjoint therapy for PTSD (San Diego Veterans Healthcare System)	Post-Traumatic Stress Disorder (PTSD)	≤ 80 mg	Yes

Source: Allucent

From symptomatic to disease-modifying treatments

The transition from symptomatic relief to disease-modification is the most significant paradigm shift in CNS therapeutics in decades.

Recent Alzheimer's approvals offer hope, but room to improve

The approvals of Leqembi (generic name: lecanemab) in January 2023 and Kisunla (generic name: donanemab) in July 2024 mark the end of a two-decade drought in Alzheimer's disease drug approvals, representing the first disease-modifying therapies to receive full FDA approval for this devastating condition.

Leqembi clinical profile: in the Phase III CLARITY-AD trial, lecanemab demonstrated a 27% slowing of cognitive decline compared to placebo over 18 months in patients with early Alzheimer's disease. While statistically significant, this translates to a relatively modest clinical benefit, with patients experiencing around five months less cognitive decline over the 18-month study period. The treatment requires bi-weekly intravenous infusions and carries significant safety concerns, with 12.6% of patients experiencing brain swelling (ARIA-E) and 17% experiencing brain bleeding (ARIA-H).

Kisunla clinical profile: Donanemab showed a 35% slowing of disease progression in the Phase III TRAILBLAZER-ALZ 2 trial, representing a somewhat greater effect than lecanemab. However, the clinical meaningfulness remains debated, with patients gaining around four to seven months of maintained function over an 18-month period. Safety concerns are similar to lecanemab, with amyloid-related imaging abnormality (ARIA) rates of 24% for brain swelling and 31% for microhaemorrhages.

Reality versus clinical trial efficacy: both treatments demonstrate that while disease-modifying effects are achievable, they are far from curative. The benefits observed in highly controlled clinical trials may be difficult to replicate in real-world practice, where patient monitoring is less intensive and adherence may be suboptimal. The requirement for regular MRI monitoring to detect ARIAs, combined with the need for specialised infusion centres, creates substantial practical barriers to widespread implementation.

Market adoption challenges: despite regulatory approval, uptake has been slower than anticipated. The limited clinical benefit, high cost ($35,000–43,000 annually) and safety requirements have led to restrictive coverage policies from many insurers. The UK's NICE initially rejected both treatments, citing insufficient cost-effectiveness, though it later provided conditional approval for Leqembi in a restricted patient population.

We touch upon the significance of these factors, alongside some of the remaining limitations below:

- **Mechanism validation:** clinical confirmation that amyloid reduction can slow cognitive decline, validating decades of research into the amyloid hypothesis, though the modest effect size suggests amyloid may not be the complete answer
- **Regulatory precedent:** the approvals have established a pathway for future disease-modifying therapy approvals, with the FDA providing clear guidance on acceptable endpoints (such as the Clinical Dementia Rating-Sum of Boxes (CDR-SB) used for Leqembi) and trial designs for neurodegenerative diseases
- **Clinical infrastructure:** development of amyloid PET scanning and specialised treatment centres create the foundation for more sophisticated Alzheimer's disease care, though highlighting the resource-intensive nature of current approaches
- **Opening doors to new targets:** the modest efficacy of anti-amyloid approaches has reinforced the need for combination therapies and alternative targets. The field is increasingly exploring tau pathology, neuroinflammation, synaptic dysfunction and metabolic approaches that may provide additive or superior benefits

These approvals represent important proof-of-concept that disease-modification is possible in Alzheimer's disease, but they also highlight the substantial work remaining to develop truly transformative treatments. The experience with these first-generation disease-modifying therapies is driving innovation towards next-generation approaches that may offer greater clinical benefit with improved safety, efficacy and quality-of-life profiles.

Schizophrenia innovation

The approval of Cobenfy (formerly known as KarXT; generic name: xanomeline/trospium chloride combination) in September 2024 as the first new mechanism in schizophrenia for 35 years demonstrates the potential for breakthrough innovation in psychiatric conditions. While Cobenfy

represents a significant advancement to existing therapies, real-world implementation still faces adoption challenges, including physician familiarity with the novel mechanism and patient access considerations.

Clinical profile: Cobenfy represents a paradigm shift as the first non-dopaminergic antipsychotic, targeting muscarinic M1/M4 receptors rather than dopamine D2 receptors. In clinical trials, it demonstrated efficacy against positive symptoms of schizophrenia while potentially offering advantages in treating negative symptoms and cognitive impairment (areas where traditional antipsychotics have limited effectiveness).

Pipeline developments: the success of Cobenfy has validated novel approaches to schizophrenia treatment, with companies like Newron Pharmaceuticals advancing evenamide, a first-in-class glutamate-modulating agent specifically for TRS. Newron's pivotal Phase III ENIGMA-TRS programme is enrolling more than 1,000 patients, representing the largest global trial conducted in this indication and demonstrating the continued innovation in addressing this challenging patient population.

Implementation challenges: despite its novel mechanism and improved side effect profile, Cobenfy faces barriers including twice-daily dosing requirements, lack of long-term comparative data against established antipsychotics and the conservative prescribing patterns typical in psychiatry. Early uptake suggests positioning primarily as an option for patients who do not respond adequately to or cannot tolerate traditional antipsychotics.

This experience provides the following lessons, in terms of target diversification, improved tolerability profiles and symptom domain expansion efforts.

- Target diversification: moving beyond dopamine-centric approaches opens new therapeutic possibilities for previously challenging symptoms.
- Improved tolerability: addressing key barriers to medication adherence through novel mechanisms, although practical implementation remains challenging.
- Symptom domain expansion: potential to address positive, negative and cognitive symptoms that have been difficult to treat with traditional approaches, creating opportunities for next-generation psychiatric treatments that target multiple symptom domains simultaneously.

Pipeline developments and next-generation targets

Beyond amyloid in Alzheimer's disease

The Alzheimer's disease pipeline has diversified significantly beyond amyloid-targeting approaches:

Tau-targeting therapies – multiple antibodies and small molecules targeting neurofibrillary tangles:

- E2814 (Eisai) – monoclonal antibody in Phase III trials, which has recently been granted Fast Track designation by the FDA.
- Posdinemab (Johnson & Johnson) – investigational monoclonal antibody targeting the mid-domain of AD-specific phosphorylated tau, currently in Phase 2b Autonomy trials. The antibody is designed to bind to pathological phosphorylated tau when released from neurons and neutralise it before it can seed and spread to other neurons.

Alternative mechanisms:

- Cortisol regulation: Actinogen Medical's Xanamem targets 11β-HSD1 enzyme inhibition to control cortisol levels in brain regions where chronically elevated cortisol contributes to Alzheimer's disease progression.
- Masitinib (originally marketed under the brand name Massivet) – targeting microglia and mast cells.

- Sodium oligomannate (development code GV-971) – anti-inflammatory compound approved in China.

Synaptic dysfunction:

- AGB101 (an extended-release formulation of levetiracetam) – neuroprotection and neuroplasticity enhancement.
- Blarcamesine (being developed by Anavex under the name ANAVEX 2-73) – sigma-1 receptor agonist addressing multiple pathways.

Both sets of approvals (Leqembi and Kisunla) highlight that, while mechanistically novel treatments are now achievable, the journey from clinical trial success to meaningful patient benefit remains complex, emphasising the continued need for better treatments that offer superior efficacy, safety and practical implementation advantages.

Alpha-synuclein targeting in Parkinson's disease

Approximately 25% of the current Parkinson's disease development pipeline targets alpha-synuclein aggregation, representing diverse approaches to address this key pathological hallmark. We discuss some examples of these below.

- **Buntanetap (Annovis Bio):** completed Phase III trial targeting multiple neurotoxic proteins including alpha-synuclein, demonstrating the potential for multi-target approaches.
- **Monoclonal antibodies:** several programmes (including Roche's prasinezumab and AstraZeneca's MEDI1341) targeting different epitopes of alpha-synuclein, including approaches that target both monomeric and aggregated forms of the protein.
- **Small molecule approaches:** compounds preventing protein aggregation through various mechanisms, including stabilisation of native protein conformation and disruption of toxic oligomer formation. Examples include anle138b, which targets oligomeric alpha-synuclein aggregates and has shown promise in preclinical models, and compounds from companies like AC Immune that focus on preventing the initial misfolding events.
- **Alternative protein targets:** some companies are pursuing complementary approaches, for example, Herantis Pharma with HER-096, a neurodegenerative therapy that mimics cerebral dopamine neurotrophic factor (CDNF) activity. This entails a multi-modal approach, targeting key drivers of neurodegeneration including cellular stress, protein misfolding and inflammation, while demonstrating excellent brain penetration, as well as potential for neuroprotection and functional restoration.

The diversity of approaches in Parkinson's disease drug development reflects the complex pathophysiology of the condition, with alpha-synuclein aggregation representing an important pathway among several interconnected mechanisms that contribute to dopaminergic neuron loss and disease progression.

Evolving clinical trial landscape

Biomarker-driven development

Modern CNS trials increasingly incorporate sophisticated biomarkers, with companies like IXICO at the forefront of this transformation through its AI-driven platforms that are advancing clinical trial management and analysis. We discuss some examples of the applications of recent development below.

- **Patient selection:** using amyloid PET and tau biomarkers to identify optimal populations, with advanced imaging analysis platforms enabling more precise patient stratification than previously possible. IXICO's IXI.Ai platform processes data from global trials and precisely measures key imaging biomarkers associated with disease identification and progression.

- **Pharmacodynamic readouts:** demonstrating target engagement through fluid biomarkers and advanced neuroimaging techniques that can detect drug effects at the molecular level, providing confidence that treatments are reaching their intended targets and producing biological effects.
- **Outcome optimisation:** integrating clinical assessments with advanced biomarker analysis through sophisticated data platforms, enabling researchers to strengthen regulatory submissions by detecting subtle therapeutic effects and providing comprehensive evidence packages beyond traditional clinical measures alone. IXICO's technology has supported hundreds of neurological clinical trials and analysed hundreds of thousands of scans, demonstrating how AI-driven biomarker analysis is reducing uncertainties in CNS drug development.
- **Real-time monitoring:** advanced platforms enable continuous monitoring of disease progression and treatment response, allowing for adaptive trial designs and more efficient clinical development programmes.

The integration of AI-powered biomarker platforms is fundamentally changing how CNS trials are designed and conducted, enabling researchers to make better informed decisions earlier in the drug development process and reducing the traditional risks associated with CNS therapeutic development.

Adaptive trial designs also represent an innovative approach, reducing development timelines in the following ways:

- **Platform trials:** testing multiple compounds in single study frameworks.
- **Biomarker-adaptive designs:** modifying trial parameters based on interim biomarker analyses.
- **Synthetic control arms:** using historical data to reduce placebo requirements.

Precision medicine approaches in trials and in treatment

Genetic stratification is becoming standard practice across CNS drug development efforts, with companies increasingly designing trials around specific genetic subpopulations with the goal of improving success rates and enabling personalised treatment approaches.

APOE4 stratification in Alzheimer's disease trials: the APOE4 gene variant, present in approximately 25% of the population, significantly increases the risk of Alzheimer's disease and affects treatment response. Companies are now routinely stratifying trials based on APOE4 status.

- **Leqembi and Kisunla trials:** both pivotal studies stratified patients by APOE4 status, revealing that homozygous APOE4 carriers (APOE4/4) have substantially higher rates of brain swelling (ARIA), coming in at c 40%, compared to 10–15% in non-carriers. This has led to enhanced monitoring protocols and modified dosing recommendations for APOE4 carriers.
- **Next-generation approaches:** emerging trials are exploring whether APOE4 carriers might benefit from different therapeutic targets entirely, with some companies developing APOE4-specific interventions.

GBA mutation screening for Parkinson's disease studies: mutations in the GBA gene (encoding glucocerebrosidase) are found in approximately 5–10% of Parkinson's disease patients, and are associated with more rapid disease progression and earlier cognitive decline.

- **Ambroxol development:** ambroxol, a mucolytic drug that can enhance glucocerebrosidase activity, has been explored in clinical studies for GBA-positive Parkinson's disease patients. The drug has shown promise in early trials and is entering Phase III development.
- **Substrate reduction therapy:** companies are developing approaches to reduce the accumulation of glucosylceramide in GBA mutation carriers, with trials specifically enrolling patients based on genetic status.

Pharmacogenomic testing for neuropsychiatric treatment approaches: The field is moving towards genetic testing to predict drug response and avoid adverse effects.

- **CYP2D6 and CYP2C19 testing:** these cytochrome P450 enzymes metabolise many neuropsychiatric medications. Patients with ultra-rapid or poor metaboliser genotypes may require dose adjustments or alternative treatments. Clinical guidelines now recommend testing before initiating certain antidepressants and antipsychotics.
- **Compass Pathways' COMP360:** the company's psilocybin trials incorporate pharmacogenomic assessments to understand how genetic variations in serotonin receptors and metabolic enzymes affect treatment responses and optimal dosing.
- **Novel targets based on genetics:** companies are developing treatments specifically for patients with rare genetic variants. For example, treatments are targeting specific ion channel mutations in certain forms of epilepsy. Saniona utilises its capabilities in ion channels and genetic considerations – and mutations in epilepsy in particular – to develop innovative new drug candidates.

The evolution towards precision medicine in CNS conditions represents a fundamental shift from the traditional 'one size fits all' approach to treatments tailored to individual genetic profiles, offering the potential for both improved efficacy and reduced adverse effects across the spectrum of neurological and psychiatric conditions.

Big pharma's return to neuroscience

After a decade of retreat from CNS research, major pharmaceutical companies are returning, with significant investments and strategic commitments.

Historical context: The great exodus

During the 2010s, numerous pharmaceutical giants abandoned or significantly reduced their neuroscience programmes in what became known as 'the great exodus' from CNS research:

Eli Lilly is perhaps the most striking example of this retreat. Despite its pioneering work in depression and being the company that developed Prozac (one of the most successful psychiatric medications in history), Lilly dramatically scaled back its neuroscience operations following a series of Alzheimer's disease failures. Its solanezumab programme, which targeted amyloid plaques, failed in multiple large Phase III trials despite initial promise. Combined with the broader challenges associated with CNS drug development, these failures led to significant workforce reductions and the closure of key neuroscience research programmes. The psychological impact on the organisation was profound, as Lilly had built much of its identity around CNS innovation.

Pfizer took perhaps the most dramatic action, closing major CNS research sites in the UK and US, following repeated late-stage clinical failures across multiple therapeutic areas. Its neuroscience division had been responsible for developing some of the world's most prescribed psychiatric medications, but a string of Phase III failures in Alzheimer's disease, depression and schizophrenia led to a complete exit from the field. Pfizer's decision sent shockwaves through the industry, as it demonstrated that even companies with strong CNS expertise and substantial resources could not overcome the fundamental challenges facing the field. The closure resulted in hundreds of job losses and the abandonment of promising early-stage programmes.

GSK reduced its neuroscience focus after achieving only limited success relative to its investment in the area. Despite having a strong heritage in CNS research and several marketed products, GSK concluded that the risk-adjusted returns in neuroscience were insufficient compared to other therapeutic areas. It shifted resources towards areas where it had greater competitive advantages, including vaccines and HIV treatments. This strategic pivot reflected a broader industry trend

towards focusing on therapeutic areas with higher success probabilities and clearer regulatory pathways.

AstraZeneca made a strategic decision to shift resources away from CNS towards oncology, where it saw greater opportunities for breakthrough innovation. Its exit was particularly notable because it occurred during a period when the company was achieving significant success in oncology with drugs like Tagrisso and Lynparza. The stark contrast between the success rates in oncology compared to CNS conditions made the strategic choice clear, although it meant abandoning years of neuroscience research and development infrastructure.

Bristol Myers Squibb scaled back psychiatric drug development despite having historical strengths in the area. It had achieved success with antipsychotic medications but faced increasing challenges in developing next-generation treatments. The decision to reduce its CNS focus was part of a broader portfolio rationalisation that saw resources redirected towards immunology and oncology, areas where the company had developed core competencies and saw a clearer path to commercial success.

This exodus was driven by a combination of factors that made CNS drug development uniquely challenging:

- **High failure rates** posed the most immediate threat to shareholder value. CNS compounds demonstrated a 93.8% failure rate compared to 86.7% for non-CNS compounds (2014 Tufts Center study), meaning that for every successful CNS drug, companies typically had to absorb the costs of 15–20 failed programmes. This failure rate was particularly devastating given the high costs associated with CNS drug development, where Phase III trials often required thousands of patients to be followed for multiple years. The cumulative financial impact of these failures often exceeded the resources that even large pharmaceutical companies were willing to commit to a single therapeutic area.
- **Long development timelines** of 15–20 years from discovery to approval created additional strategic challenges. In rapidly evolving pharmaceutical markets, companies needed to balance long-term CNS investments against shorter-term opportunities in other therapeutic areas. The extended timelines also meant that CNS programmes often spanned multiple changes in corporate strategy and leadership, making it difficult to maintain consistent support for programmes through inevitable setbacks and delays. The opportunity cost of tying up resources for such extended periods became increasingly difficult to justify to investors focused on quarterly performance metrics.
- **Unclear regulatory pathways** for novel mechanisms created additional uncertainty. Unlike oncology, where biomarkers and accelerated approval pathways provided clearer routes to market, CNS conditions lacked well-established surrogate endpoints that regulators would accept. This regulatory uncertainty meant that companies could invest heavily in programmes only to discover late in development that their chosen endpoints would not support approval. The lack of precedent for novel mechanisms made it difficult to design trials with confidence, leading to repeated late-stage failures as companies struggled to demonstrate clinically meaningful benefits using available assessment tools.
- **High development costs** of c $3–4bn per approved CNS drug reflected both the high failure rates and complexity of CNS clinical trials. These trials typically required large patient populations, extended treatment periods and sophisticated endpoint assessments. The costs were further inflated by the need for specialised clinical infrastructure, including brain imaging facilities and expert clinical sites capable of managing complex CNS patient populations. When combined with high failure rates, the risk-adjusted investment required for CNS drug development often exceeded what companies could justify to shareholders, particularly when more attractive opportunities existed in other therapeutic areas.

Recent M&A activity and future strategic rationale

The landscape has changed dramatically, with more than $50bn in neuroscience transactions over the past couple of years:

Major acquisitions

- **Johnson & Johnson/Intra-Cellular Therapies:** $14.6bn acquisition (a 39% premium) brings commercial antipsychotic Caplyta and pipeline assets.
- **Bristol Myers Squibb/Karuna Therapeutics:** $14.0bn (a 53% premium) for breakthrough schizophrenia treatment (now Cobenfy).
- **AbbVie/Cerevel Therapeutics:** $8.7bn bet (a 22% premium) on neurological pipeline (subsequently impaired following clinical failures).
- **Novartis/DTx Pharma:** $500m for precision psychiatry platform.

Strategic licensing deals

- **AbbVie/Gilgamesh Pharmaceuticals:** $0.65–1.95bn licensing agreement for neuroplastogens. This deal provides AbbVie with exclusive rights to Gilgamesh's portfolio of next-generation psychedelic compounds designed to provide therapeutic benefits without hallucinogenic effects. The programmes are in preclinical development, focusing on novel neuroplastogen molecules that could offer the neuroplasticity benefits of traditional psychedelics while avoiding the perceptual distortions that complicate clinical administration.
  - The partnership recently developed with AbbVie's $1.2bn acquisition of Gilgamesh's bretisilocin (for major depressive disorder).
- **Takeda/AC Immune:** $0.1–2.1bn deal for Alzheimer's disease programmes. This collaboration focuses on ACI-24.060, AC Immune's anti-amyloid beta active immunotherapy currently in Phase Ib/II trials. ACI-24.060 is designed to induce a robust antibody response against toxic forms of amyloid beta believed to drive plaque formation and Alzheimer's disease progression. The agreement also encompasses AC Immune's broader platform for developing active immunotherapies targeting amyloid pathology.
- **Bristol Myers Squibb/Prothena:** $80–617.5m licensing agreement for one of Prothena's neurological programmes (PRX019, Phase I at the time of this agreement). The broader partnership focuses on Prothena's pipeline of investigational therapies for neurodegenerative diseases.
- **Novartis/Arrowhead Pharmaceuticals:** $0.2–2bn licencing and collaboration agreement for ARO-SNCA, Arrowhead's siRNA therapy against alpha-synuclein for the treatment of synucleinopathies such as Parkinson's disease, and for other additional collaboration targets that will utilise Arrowhead's proprietary TRiM platform. The programmes involved were in the preclinical stage of development at the time of the deal.

These deals demonstrate the substantial premiums that big pharma is willing to pay for access to novel CNS approaches, even at relatively early stages of development. The willingness to commit such significant resources to preclinical and early clinical programmes reflects both the substantial unmet need in CNS conditions and the recognition that breakthrough approaches may be necessary to achieve meaningful therapeutic advances in these challenging conditions.

Patent cliff pressures

The pharmaceutical industry faces an unprecedented patent cliff, with more than $200bn in annual revenue at risk between 2024 and 2030 (based on Evaluate Pharma data). Major patent expiries lead to the following factors at play in the big pharma landscape:

- multiple blockbuster drugs across therapeutic areas losing exclusivity;
- limited pipeline replacement in traditional areas; and
- increasing generic and biosimilar competition.

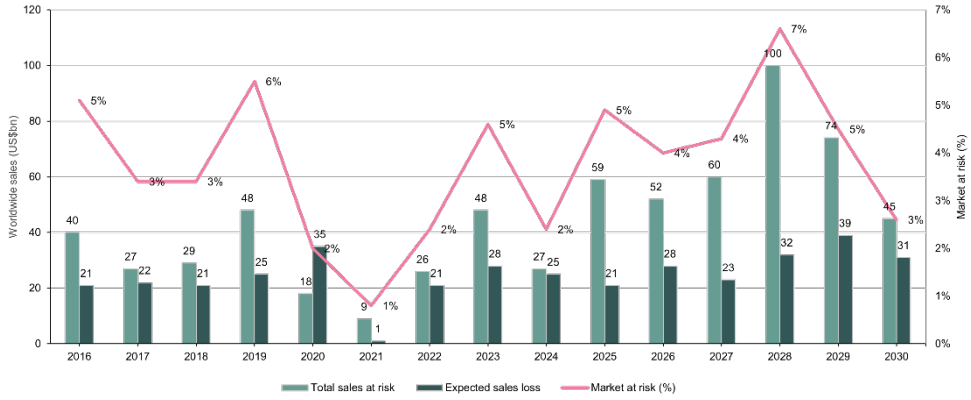
With these pressures, we believe the CNS renaissance could lead to CNS-focused biotechs being likely targets of future M&A activity. We discuss below some key factors at play.

CNS as growth driver: neuroscience offers attractive characteristics for addressing patent cliff pressures, driven by significant unmet medical need where even existing treatments often fail to halt disease progression. In conditions like Alzheimer's disease and Parkinson's disease, patients continue to decline despite available therapies, highlighting the substantial market opportunity for more effective interventions. This makes the CNS an increasingly strategic focus for pharmaceutical companies seeking sustainable growth in areas with clear therapeutic gaps.

Large addressable markets: CNS conditions affect billions of people globally, creating substantial commercial opportunities that can support blockbuster drug development. Alzheimer's disease alone affects more than 55 million people worldwide and is projected to reach 78 million by 2030, while depression affects more than 280 million people globally. The scale of these patient populations means that even modest market penetration can generate significant revenues, making CNS an attractive area for companies seeking to replace revenue from patent-expiring products.

Limited competition: few effective treatments exist in many CNS indications, creating opportunities for first-mover advantages and market leadership positions. Unlike therapeutic areas like cardiovascular disease or diabetes where numerous effective treatments compete, many CNS conditions have minimal therapeutic options. TRD affects approximately one-third of depression patients but has very limited approved therapies. Similarly, neurodegenerative diseases like Huntington's disease and frontotemporal dementia have limited disease-modifying treatment options, creating substantial opportunities for companies that can develop more effective therapies.

Exhibit 10: The biopharma industry faces a major drop in patented revenues



Source: Edison Investment Research; Evaluate Pharma.

Pricing power: high unmet need supports premium pricing for effective therapies, with healthcare systems and patients willing to pay substantial amounts for treatments that can meaningfully affect devastating conditions. Recent CNS drug approvals demonstrate this pricing power, with Leqembi and Kisunla priced at $26,500–$32,000 annually, despite modest clinical benefits. Rare disease CNS treatments command even higher prices, with Zolgensma (for spinal muscular atrophy) priced at more than $2.1m per treatment. The willingness of healthcare systems to fund these treatments reflects the substantial economic and social cost of CNS conditions.

Long development visibility: the extended development timeline of CNS therapies provides companies with long-term revenue visibility once a programme reaches late-stage development. While this timeline creates challenges during development, it also means that successful CNS franchises can provide stable revenue streams for extended periods, helping pharmaceutical companies plan long-term growth strategies and justify substantial R&D investments. Moreover, these lengthy development cycles create significant barriers to entry for potential competitors, as the substantial time and capital requirements deter many companies from entering established

therapeutic areas. These characteristics combine to make CNS an attractive therapeutic area for big pharma companies seeking to replace revenue from patent-expiring products, although success requires substantial investment in research capabilities and risk tolerance for the inherent challenges of neurological drug development.

Investment landscape and opportunities

The CNS investment landscape has transformed dramatically, with renewed venture capital interest and diverse public market opportunities.

Venture funding revival

After years of limited investment, CNS start-ups attracted significant venture capital in 2024:

- **$1.7bn total investment:** an 80% increase on the previous year.
- **Third-largest speciality:** behind oncology and immunology in venture funding.
- **Early 2025 momentum:** approximately $325m raised in January 2025 alone.

We summarise below the key investment themes currently shaping this space:

- **Drug delivery systems and novel targets:** BBB-crossing and precision targeting technologies that enable therapeutic molecules to reach brain targets previously considered inaccessible.
- **AI-driven drug discovery:** platform companies applying machine learning to enhance target identification, patient stratification and clinical trial optimisation.
- **Biomarker platforms:** diagnostic and monitoring technologies that enable precision medicine approaches and improve clinical trial success rates.

This ordering reflects the logical progression from the fundamental technological breakthrough (BBB crossing) that enables CNS drug development, through to the tools that enhance development efficiency (AI and biomarkers), alongside the emerging therapeutic modalities that these enabling technologies make possible.

Public market opportunities

We highlight here two dedicated neuroscience ETFs, specialised to provide broad CNS drug development exposure:

- **iShares Neuroscience and Healthcare ETF (IBRN):** 52 holdings, launched in August 2024 (1.59% year-to-date total return); and
- **TEMA Neuroscience and Mental Health ETF (MNTL):** 47 holdings, launched in January 2024 (-4.42% year-to-date total return).

Top holdings include established players (Eli Lilly, Biogen) and emerging specialists (Intra-Cellular Therapies, Vertex Pharmaceuticals).

Individual company opportunities

The public markets offer exposure across the CNS value chain. We present some examples below:

Large-cap established

- **Biogen:** leading Alzheimer's disease franchise with Leqembi;
- **Eli Lilly:** Kisunla launch and broader neurodegeneration pipeline; and
- **Bristol Myers Squibb:** Cobenfy commercialisation and psychiatric portfolio.

Mid-cap specialists

- **Neurocrine Biosciences:** established CNS portfolio with tardive dyskinesia and Parkinson's disease treatments;
- **Sage Therapeutics:** depression and neurological pipeline; and

- **Compass Pathways:** leading psychedelic development.

Small-cap innovation

- **Denali Therapeutics:** BBB-crossing platform technology;
- **Annovis Bio:** multi-target neurodegeneration approach; and
- **Cybin:** deuterated psychedelics in late-stage development.

Risk-reward considerations

Investment risks

Despite improved prospects, CNS investments carry inherent risks.

Clinical development risks:

- **High failure rates persist:** even with better tools, CNS trials remain challenging.
- **Long development timelines:** 10–15 years from discovery to approval.
- **Regulatory uncertainty:** novel mechanisms face unknown approval pathways.

Commercial risks:

- **Payer resistance:** high-cost CNS treatments face reimbursement challenges, particularly given the modest clinical benefits demonstrated by first-generation, disease-modifying therapies.
- **Market access barriers:** specialised administration requirements limit adoption, with many CNS treatments requiring infusion centres, regular monitoring or specialised clinical expertise.
- **Regulatory and safety requirements:** complex monitoring protocols and safety considerations can create additional barriers to widespread implementation.

Company-specific risks:

- **Single asset dependence:** many biotech companies rely on single programmes.
- **Funding requirements:** long development cycles require substantial capital.
- **Key person risk:** departure of scientific founders can affect programmes.

Mitigating factors

Several factors help mitigate traditional CNS investment risks.

Improved target validation:

- **Proof of concept:** recent approvals validate previously unproven mechanisms.
- **Biomarker confirmation:** better tools for demonstrating drug activity.
- **Genetic insights:** human genetics provide stronger target validation.

Market opportunities:

- **Ageing demographics:** growing patient populations ensure expanding markets.
- **Limited competition:** few effective treatments in most CNS indications.
- **High unmet need:** payers increasingly willing to fund effective treatments.

Technology advantages:

- **AI-driven efficiency:** reduced development costs and timelines.
- **Platform approaches:** single technologies applicable across multiple indications.
- **Partnership opportunities:** big pharma seeking external innovation.

Investment conclusion

The CNS renaissance represents one of the most compelling investment themes in healthcare today, driven by a unique convergence of technological breakthroughs, novel mechanisms and substantial unmet medical need. The transformation from symptomatic treatments to disease-modifying therapies marks a paradigm shift comparable to the oncology revolution of the past two decades.

Several factors make the current investment environment particularly attractive. The BBB breakthrough technologies are fundamentally changing what is therapeutically possible in CNS conditions. AI and biomarker advances are reducing development risks and improving success probabilities. Big pharma's $50bn re-engagement provides both validation and partnership opportunities for innovative companies.

The market opportunity is substantial, with CNS conditions now affecting more than 3.4 billion people globally and creating an economic burden that one study puts at $800bn pa in the US alone. The ageing global population ensures a growing addressable market, while limited existing effective treatments create significant pricing power for breakthrough therapies.

For investors, the CNS renaissance offers multiple avenues for exposure. Large-cap pharmaceutical companies provide stability and diversified pipelines, while mid-cap specialists offer focused exposure to specific mechanisms or disease areas. Small-cap biotechnology companies present the highest risk-reward opportunities, particularly those with platform technologies applicable across multiple indications.

The companies showcased in this report represent the breadth of innovation across the CNS landscape. From BBB-crossing technologies and precision protein modulation to synthetic psychedelics and AI-driven biomarker platforms, these companies are addressing fundamental challenges that have historically limited CNS therapeutic development.

Risk mitigation strategies include diversification across development stages, therapeutic areas and company sizes. The improved success probabilities from better tools and validated mechanisms, combined with substantial partnership interest from major pharmaceutical companies, help offset traditional biotech risks.

As the CNS renaissance continues to unfold, investors who position themselves early in this transformation stand to potentially benefit from one of healthcare's most significant paradigm shifts. The combination of technological breakthroughs, regulatory precedent and massive unmet need creates a compelling investment landscape that is likely to generate substantial returns for those who navigate it successfully.

The current landscape provides many levers for a potentially compelling investment opportunity. The technological foundations are in place, the regulatory pathways are established and the market opportunity is vast. For investors seeking exposure to transformative healthcare innovation, the CNS renaissance offers exceptional potential for both financial returns and positive patient impact.

Appendix: Company showcase

The following companies are those we have identified as possessing particularly innovative approaches to addressing key challenges in CNS drug development, each contributing unique solutions to transform treatment paradigms. (Edison clients are indicated with an asterisk).

AC Immune

Precision immunotherapy targeting multiple neurodegenerative pathways

Company overview: AC Immune (NASDAQ: ACIU) is a Swiss clinical-stage biopharmaceutical company pioneering precision medicine for neurodegenerative diseases through its SupraAntigen and Morphomer technology platforms. The company advances one of the industry's broadest clinical-stage pipelines with three active immunotherapies currently in Phase II trials across Alzheimer's disease and Parkinson's disease.

Addressing strategic challenges: traditional approaches targeting single pathological proteins like amyloid have shown limited clinical success, while more than 315 million people globally live with preclinical Alzheimer's disease requiring earlier intervention according to the company. Current Parkinson's disease treatments only address symptoms rather than the underlying alpha-synuclein pathology driving neurodegeneration.

Innovative solution: AC Immune's SupraAntigen platform generates antibodies with unique binding properties that preferentially target pathological forms of disease-causing proteins including tau, alpha-synuclein and amyloid beta. The company's active immunotherapy approach aims to harness patients' immune systems to generate targeted antibodies similar to vaccines for infectious diseases. The Morphomer platform enables development of first-in-class PET tracers and small molecules targeting multiple neurodegenerative pathways.

Clinical progress: AC Immune's lead programme ACI-35.030 has advanced to a potentially registration-enabling Phase IIb trial (ReTain) in partnership with Janssen (JNJ), evaluating tau immunotherapy in 500 preclinical Alzheimer's disease patients over four years. The company's Parkinson's disease programme ACI-7104.056 is advancing through Phase II trials with no safety concerns reported to date, while ACI-24.060 for Alzheimer's disease continues Phase Ib/II studies.

Actinogen Medical*

Targeting Alzheimer's disease through cortisol regulation

Company overview: Actinogen Medical (ASX: ACW) is developing Xanamem (emestedastat), a novel oral therapy for Alzheimer's disease and depression, currently at the stage of late clinical development.

Addressing strategic challenges: Current Alzheimer's disease treatments are modestly effective at best, often require inconvenient administration and carry significant side effects. There remains a substantial unmet need for safer and more effective oral therapies.

Innovative solution: Xanamem employs a novel mechanism controlling cortisol levels in important brain areas through inhibition of the 11β-HSD1 enzyme, without blocking normal cortisol production outside the brain. This first-in-class, once-daily pill targets brain regions where chronically elevated cortisol contributes to Alzheimer's disease progression and neuronal toxicity.

Clinical progress: Xanamem has been studied in eight clinical trials with more than 400 people treated, demonstrating a promising safety and efficacy profile. The ongoing XanaMIA Phase IIb/III trial is enrolling 220 participants with biomarker-positive mild to moderate Alzheimer's disease across Australia and the US.

See below for our most recently conducted Edison TV executive interview with Actinogen Medical.

Exhibit 11: Actinogen Medical – executive interview with CEO Dr Steven Gourlay

Source: Edison Investment Research

Alzinova

Innovative immunotherapy targeting toxic amyloid oligomers

Company overview: Alzinova (NFNPGM: ALZ) is a Sweden-based clinical-stage biopharmaceutical company developing first-in-class immunotherapies for Alzheimer's disease using its proprietary AβCC Peptide Technology. The company's lead candidate, ALZ-101, is approaching Phase II trials, with a more specific preclinical candidate ALZ-201 under development.

Addressing strategic challenges: Historical Alzheimer's immunotherapy approaches have failed due to the heterogeneous nature of neurotoxic Aβ42 oligomers and the inability to specifically target the most harmful protein aggregates. Current approved treatments provide only modest symptomatic relief without necessarily addressing underlying disease mechanisms, leaving patients with limited therapeutic options and continued cognitive decline.

Innovative solution: Alzinova's AβCC Peptide Technology produces conformational restriction of Aβ42 proteins, creating stable oligomeric structures that can be precisely targeted with immunotherapy. ALZ-101 combines this technology with a vaccine approach, generating antibodies specifically against toxic amyloid-beta oligomers while avoiding non-specific plaque binding. This first-in-class approach targets the root cause of neurodegeneration rather than downstream effects, potentially offering superior safety compared to antibody therapies that cause ARIA complications.

Clinical progress: ALZ-101 has completed a successful Phase Ib trial in 26 patients with early Alzheimer's disease, demonstrating excellent safety and tolerability with no ARIA-related complications. The study showed robust immune responses in over 95% of patients, with exploratory analysis indicating stable disease progression and potential cognitive benefits. An Investigational New Drug application for Phase II was submitted in August 2025, with regulatory clearance expected in H2 2025. The company raised SEK30.3m through a rights issue in 2025, providing financial runway into 2026 while pursuing partnership opportunities with major pharmaceutical companies.

Anavex Life Sciences

Targeting neurodegeneration through precision medicine

Company overview: Anavex Life Sciences (NASDAQ: AVXL) is developing precision medicine treatments for neurodegenerative and neuropsychiatric conditions through its SIGMACEPTOR discovery platform, with lead candidate blarcamesine showing promising results in Alzheimer's disease and other CNS conditions.

Addressing strategic challenges: current Alzheimer's disease treatments provide limited disease-modifying effects and often require inconvenient administration methods. Patients and neurologists prefer convenient, orally available treatment options that can be accessed without logistical restrictions. There remains substantial unmet need for therapies that address multiple CNS pathologies through upstream mechanisms.

Innovative solution: blarcamesine (ANAVEX 2-73) is an orally available, once-daily small molecule that activates the sigma-1 receptor (SIGMAR1) to restore cellular homeostasis and enhance autophagy – a key clearance mechanism for protein aggregates and misfolded proteins. This upstream approach targets the root causes of neurodegeneration rather than just the symptoms.

Clinical progress: blarcamesine successfully completed a landmark Phase IIb/III trial in early Alzheimer's disease, demonstrating a 36.3% slowing of clinical progression at 48 weeks with a favourable safety profile and no neuroimaging adverse events. The company has filed for approval with the European Medicines Agency. Long-term data show continued benefit over four years of treatment, with 74 patients currently receiving blarcamesine through compassionate use programmes.

ATAI Life Sciences

Pioneering psychedelic mental health therapeutics

Company overview: ATAI Life Sciences (NASDAQ: ATAI) is developing a comprehensive pipeline of novel psychedelic and non-psychedelic compounds for treatment-resistant mental health conditions, with multiple assets in Phase II clinical development and a planned merger with Beckley Psytech (expected to close in Q425) intended to form a global leader in psychedelic therapies.

Addressing strategic challenges: traditional mental health treatments show limited efficacy in TRD, anxiety and other psychiatric conditions, often requiring complex administration protocols and carrying significant side effects. Patients suffering from these debilitating conditions urgently need innovative, rapid-acting therapeutic options.

Innovative solution: ATAI's differentiated approach leverages psychedelic compounds with convenient routes of administration and short time-in-clinic requirements. Key assets include VLS-01 (buccal film DMT) designed for a two-hour treatment paradigm, EMP-01 (oral R-MDMA) with expected improved tolerability compared to racemic MDMA and BPL-003 (intranasal 5-MeO-DMT) for rapid-acting antidepressant effects.

Clinical progress: ATAI has dosed the first patient in Phase II trials for both VLS-01 and EMP-01, with top-line data expected in Q126. The company announced positive top-line results from Beckley Psytech's Phase IIb study of BPL-003 in TRD in July 2025, with the 8mg and 12mg doses demonstrating statistically significant reductions in depressive symptoms (12.1 and 11.1 point MADRS improvements respectively) that were maintained for eight weeks following a single dose. This represents the largest controlled trial of 5-MeO-DMT (source: atai/Beckley Psytech press release). The planned merger with Beckley Psytech is expected to close in Q425, intended to create a market-leading platform with a cash runway through multiple Phase II catalysts.

BioArctic

Pioneering brain delivery technology

Company overview: BioArctic (OMX: BIOA) is a Swedish research-based biopharma company focusing on innovative treatments that can delay or stop the progression of neurodegenerative diseases. The company is the originator of Leqembi (lecanemab).

Addressing strategic challenges: less than 1% of antibodies targeting CNS conditions reach the brain due to the BBB. The next generation of treatments requires different modalities coupled with technology to transport treatments across the BBB and into the brain.

Innovative solution: BioArctic's proprietary BrainTransporter technology platform uses the transferrin receptor to facilitate the uptake of antibodies, proteins and other substances in the brain. The technology has shown up to 70 times greater brain exposure of amyloid beta antibodies in non-human primates, potentially yielding better efficacy, fewer side effects and lower doses.

Clinical progress: BioArctic recently signed a licensing agreement with Bristol Myers Squibb regarding the company's PyroGlu-Aβ antibody portfolio, including a project utilising the BrainTransporter technology. The company also has a research collaboration agreement with Eisai on a non-disclosed Alzheimer's disease drug coupled with the BrainTransporter technology.

Compass Pathways

Synthetic psilocybin for mental health

Company overview: Compass Pathways (NASDAQ: CMPS) is a biotechnology company dedicated to accelerating patient access to evidence-based innovation in mental health. It is pioneering a new paradigm for treating mental health conditions focused on rapid and durable responses through the development of investigational synthetic psilocybin treatment (COMP360).

Addressing strategic challenges: the United States is in a mental health crisis, with depression one of the most common mental health conditions. Due to the limitations of approved existing medications, approximately one-third of patients with major depressive condition will develop TRD.

Innovative solution: COMP360 is a synthetic, proprietary formulation of psilocybin under investigation for difficult-to-treat mental health conditions. The programme aims to evaluate the safety and efficacy of COMP360 psilocybin for TRD through two pivotal Phase III trials, COMP005 and COMP006.

Clinical progress: the ongoing COMP005 trial has dosed 258 participants with TRD across 32 sites in the United States. The COMP006 trial is running in parallel with 568 planned participants from North America and Europe. Compass anticipates sharing 26-week data for COMP005 once all participants in the COMP006 trial have completed part A, with 26-week data from COMP006 expected in the second half of 2026.

Denali Therapeutics

Engineering BBB delivery for neurodegeneration

Company overview: Denali Therapeutics (NASDAQ: DNLI) is a biopharmaceutical company developing a broad portfolio of product candidates engineered to cross the BBB for neurodegenerative diseases. It maintains strong financial resources, with approximately $0.9bn in cash at 30 June 2025 extending the runway into 2028.

Addressing strategic challenges: As stated above, the BBB severely limits therapeutic delivery of most CNS drugs. This fundamental delivery challenge has been a major obstacle, preventing effective CNS drug development across multiple neurodegenerative conditions.

Innovative solution: Denali's proprietary transport vehicle (TV) technology platform engineers BBB receptor binding into therapeutic molecules through receptor-mediated transcytosis, specifically targeting the transferrin receptor without disrupting normal transferrin binding. The platform includes multiple modalities: Antibody Transport Vehicle (ATV), Protein Transport Vehicle (PTV) and Enzyme Transport Vehicle (ETV) for delivering different therapeutic classes across the BBB.

Clinical progress: Denali's most advanced programme BIIB122 (DNL151), a small molecule LRRK2 inhibitor developed with Biogen for Parkinson's disease, is being evaluated in the Phase IIb LUMA study enrolling approximately 640 early-stage patients. The company completed enrolment for the LUMA study in May 2025, with a readout expected in 2026, while also advancing TV-enabled programmes including DNL593 for frontotemporal dementia and DNL310 for Hunter syndrome.

Harness Therapeutics

Precision protein modulation for Huntington's disease

Company overview: Harness Therapeutics (private) is leveraging its MISBA platform for fine-tuned protein synthesis modulation to develop disease-modifying therapies for neurodegenerative conditions.

Addressing strategic challenges: Huntington's disease is a devastating inherited condition with no disease-modifying treatments. Historical approaches targeting mutant Huntingtin protein alone have proved insufficient, while complex pathways require very controlled therapeutic adjustments that existing platforms cannot achieve.

Innovative solution: the MISBA platform enables unprecedented precision in protein synthesis control, targeting somatic expansion – the process driving accelerating CAG repeat tract expansion. The company's antisense oligonucleotides drive controlled increases in FAN1 nuclease by blocking miRNA degradation, significantly slowing somatic expansion in patient-derived neuronal models.

Clinical progress: Harness plans to select a development candidate by end-2025 and initiate clinical testing in early 2027, with the aim that this work will deliver the first disease-modifying therapy for people with Huntington's disease. Beyond its lead programme, Harness is pursuing compelling upregulation targets for ALS, Alzheimer's disease and Parkinson's disease.

Herantis Pharma*

Pioneering neuroregenerative therapy for Parkinson's disease

Company overview: Herantis Pharma (HEL: HRTIS) is developing HER-096, a first-in-class neuroregenerative drug candidate designed to stop the progression of Parkinson's disease and repair striatal damage.

Addressing strategic challenges: despite decades of research, no approved disease-modifying treatments exist for Parkinson's disease, which affects more than 10 million people worldwide. The BBB presents a major obstacle, preventing most therapeutic molecules from reaching affected brain regions.

Innovative solution: HER-096 is a small peptide that mimics CDNF activity (CDNF is believed to protect dopaminergic neurones and restore function to degraded neurons, with potential to address both motor and non-motor symptoms of PD, while also slowing or stopping disease progression). Its multi-modal mechanism targets key drivers of neurodegeneration including cellular stress, protein misfolding and inflammation. Crucially, HER-096 demonstrates excellent brain penetration due to its small size compared to CDNF and other biologics.

Clinical progress: currently in Phase Ib trials assessing safety and tolerability of repeated subcutaneous dosing in Parkinson's patients, building on positive Phase Ia results demonstrating

favourable safety and effective brain penetration. The programme is supported by 15 years of research and validation from external bodies including the Michael J. Fox Foundation and Parkinson's UK.

See below for our most recently conducted Edison TV executive interview with Herantis Pharma.

Exhibit 12: Herantis Pharma – executive interview with CEO Dr Antti Vuolanto

Source: Edison Investment Research

IXICO

AI-driven imaging and biomarker analytics

Company overview: IXICO (LSE: IXI) is a global leader in neuroscience imaging and biomarker analytics, building expertise, services and proprietary technology in the neurological treatment renaissance.

Addressing strategic challenges: success in treating CNS disease depends on fully realising the promise of precision medicine. The development of reliable biomarkers has been a key historical barrier to successful CNS drug development.

Innovative solution: the company's proprietary AI-driven IXI.Ai platform for neurological clinical trial management and analysis helps advance the treatment of neurological conditions and reduce the uncertainties associated with drug discovery, development and monitoring. The platform reliably processes data from global trials, precisely measuring key imaging biomarkers associated with the identification, progression and treatment of diseases.

Clinical progress: IXICO's technology and expertise is being used across the globe, and has supported hundreds of neurological clinical trials, analysed hundreds of thousands of scans and built an expansive network of expert imaging centres worldwide. The latest generation of the IXI.Ai platform positions the company beyond its traditional iCRO remit into diagnostics and clinical decision support.

Nevrargenics

Developing novel drugs to reverse neurodegenerative diseases

Company overview: Nevrargenics (private) is a biotechnology spinout company developing a series of novel drugs based on retinoid acid receptor (RAR) technology for neurodegenerative diseases affecting up to one billion people worldwide.

Addressing strategic challenges: neurodegenerative diseases are characterised by progressive loss of neurons in the CNS. There are no drugs currently available that can reverse disease in these conditions, despite the huge unmet need. There is a need for innovative compounds that can effectively target CNS cells.

Innovative solution: the company has developed RAR modulators based on the understanding that complex neurodegenerative diseases require multi-target therapeutic approaches. Rather than addressing single pathways, RAR modulators simultaneously influence multiple critical mechanisms in CNS biology. These modulators are believed to play crucial roles in CNS development and provide ongoing protection, affecting neuroinflammatory, neuroprotective and neuroplasticity pathways..

Clinical progress: Nevrargenics has identified a lead drug compound, NVG0645 (Ellorarxine), which it is manufacturing in preparation for human trials. This receptor-selective compound stimulates improved nerve cell communication and has demonstrated exceptional CNS exposure in preclinical development studies, with the potential to reverse disease by repairing neurons.

Newron Pharmaceuticals*

Revolutionising TRS

Company overview: Newron Pharmaceuticals (SIX: NWRN) is developing evenamide, a first-in-class glutamate-modulating agent for TRS, one of psychiatry's most urgent unmet needs.

Addressing strategic challenges: TRS affects nearly half of schizophrenia patients but has limited treatment options. Current antipsychotics primarily target dopamine receptors, leaving many patients unresponsive and suffering from significant side effects. Clozapine, the only approved TRS therapy, has serious side effects, which limits its utilisation in clinical settings.

Innovative solution: evenamide represents a paradigm shift as the first non-dopaminergic approach to TRS. It selectively inhibits voltage-gated sodium channels, normalising abnormal glutamate transmission while preserving basal activity. Designed as an adjunctive therapy, it eliminates the need for switching or titration from existing treatments.

Clinical progress: earlier clinical programmes demonstrated sustained benefit for TRS patients, including those who had failed multiple previous treatments. The pivotal Phase III ENIGMA-TRS programme is enrolling more than 1,000 TRS patients, representing the largest global trial conducted in this indication, to our knowledge.

See below for our most recently conducted Edison TV executive interview with Newron Pharmaceuticals.

Exhibit 13: Newron Pharmaceuticals – executive interview with CEO Stefan Weber

Source: Edison Investment Research.

Oryzon Genomics*

Pioneering epigenetic therapies for neuropsychiatric disorders

Company overview: Oryzon Genomics (BME:ORY) is a late clinical-stage epigenetics company developing first-in-class medicines, mainly looking at LSD1 inhibitors, with lead candidate vafidemstat advancing towards Phase III trials for borderline personality disorder (BPD) and showing promise across multiple neuropsychiatric and neurodevelopmental conditions including autism spectrum disorder (ASD) and schizophrenia.

Addressing strategic challenges: aggression is a prevalent and devastating symptom across severe neuropsychiatric disorders, with more than 70% of BPD patients exhibiting aggressive behaviour and more than 75% attempting suicide. In schizophrenia, 10–45% of hospitalised patients engage in violent conduct, while more than 50% of ASD children exhibit verbal or physical aggression. These behaviours complicate treatment, increase emergency care visits and impose profound clinical, familial and economic burdens, yet no approved treatments specifically target aggression in neuropsychiatric conditions.

Innovative solution: vafidemstat is a breakthrough brain-penetrant LSD1 inhibitor that resets neuronal function through a novel synaptogenic approach. The compound works by derepressing genes critical for neuronal plasticity, axonal branching and navigation while repressing neuroinflammation genes and modulating stress response pathways in the prefrontal cortex. Through this multifaceted epigenetic action, targeting the root epigenetic mechanisms underlying neuropsychiatric symptoms, vafidemstat has shown efficacy in enhancing sociability, improving memory and markedly reducing aggression in preclinical models.

Clinical progress: vafidemstat has been safely administered to more than 425 subjects for periods ranging from three to 24 months. The Phase IIa REIMAGINE basket trial demonstrated reduced agitation and aggression across ASD, BPD, and ADHD patients. The global, radomised Phase IIb PORTICO trial in BPD showed clinically meaningful improvements in aggression and overall symptoms, positioning the programme for Phase III advancement, pending regulatory approval. A randomised Phase IIb trial in schizophrenia (including negative symptoms, where the unmet need lies) is ongoing across European countries, and the company plans to launch HOPE-2, a new Phase II trial in ASD-related Phelan-McDermid Syndrome within H225. With $50m in funding

secured in 2025, Oryzon is positioned to deliver targeted therapies addressing neurodevelopmental syndromes and core symptoms in idiopathic neuropsychiatric patients.

See below for our most recently conducted Edison TV executive interview with Oryzon Genomics.

Exhibit 14: Oryzon Genomics – executive interview with CEO Carlos Buesa

Source: Edison Investment Research.

Saniona

Diversified ion channel platform with major partnerships

Company overview: Saniona (OMX: SANION) is a European pioneer in ion channel drug discovery with a broad pipeline addressing neurological conditions. The company has secured multiple major partnerships. Notably, an August 2025 deal worth up to $1.035bn (excluding royalties) with Jazz Pharmaceuticals for SAN2355, and an agreement with Acadia Pharmaceuticals worth up to $610m (excluding royalties) for SAN711 in 2024 in conditions including essential tremor.

Addressing strategic challenges: Neurological disorders such as epilepsy, major depressive disorder and obesity lack effective treatments with acceptable safety profiles. Current therapies often have significant side effects, limited efficacy, or complex administration requirements. Ion channels represent validated but technically challenging drug targets that require specialised expertise to develop selective, subtype-specific modulators.

Innovative solution: Saniona's proprietary ion channel drug discovery platform creates selective, subtype-specific, state-dependent modulators targeting GABAA, Kv7.2/Kv7.3, and other ion channel families. The platform has generated multiple differentiated candidates: SAN2355 (Kv7.2/Kv7.3 activator for epilepsy), SAN2219 (GABA-A α2/α3/α5 activator for acute seizures), SAN2465 (GABAA α5 NAM for major depressive disorder) and tesofensine (approaching regulatory approval for obesity in Mexico through partner Medix).

Clinical progress: The Jazz Pharmaceuticals deal for SAN2355 represents one of the largest preclinical agreements among Swedish biotech companies, with US$42.5m upfront and up to US$1.035bn in total milestones plus royalties. SAN2355 is expected to enter Phase I by year-end 2025. The company will initiate a Phase I study for SAN2219 in H1 2026, while SAN2465 is targeted for H2 2026. The company maintains a strong cash position of approximately SEK708m pro forma as of 30 June (including warrant proceeds and upfront payment from Jazz deal), providing a robust financial runway through multiple clinical milestones.

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