EDISON

Neuroscience comeback

Ripe for clinical innovation

Edison themes

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Over the last 20 years the development of new therapies aimed at tackling the most major chronic neurodegenerative diseases (NDD) has been filled with promise and setbacks. The complexity associated with targeting neurological diseases has led to some big pharma players retreating from brain drug research, yet the recent technological and clinical advancements exhibit potential to address the ever-growing demand. Having observed notable milestones to date in neurology and potential innovative mechanisms of action, we anticipate that we may only be a few positive studies away from the launch of the next generation of breakthrough NDD medicines.

Following in the footsteps of oncology

Many of us are acutely aware of the challenges associated with drug development. However, these challenges are perhaps most pertinent in discovering new medicines to treat central nervous system (CNS) disorders. CNS clinical programmes have historically experienced substantially higher rates of failure relative to most other disease areas, with the success rates of CNS drugs roughly less than half of those for non-CNS drugs. This is likely due to the complexity of CNS disorders, historical lack of understanding of disease pathologies and inappropriate trial designs that lacked clinically meaningful endpoints.

With recent technological and clinical advancements, we are now observing the emergence of new genetic targets to treat CNS diseases, effective biomarkers to de-risk programmes earlier during discovery, delivery platforms that get drugs into the brain and more sophisticated trial designs that focus on meaningful benefits to patients. We feel neuroscience drug discovery could be at the beginning of a major evolution where the breakthroughs we are seeing today, and further anticipate in the 2020s, closely resemble what drove the successes seen in oncology in the 2010s with immunoncology and checkpoint inhibitors.

Being driven by the science is key

While we are not able to predict the timing of the next CNS breakthrough, it is clear that it will be a collective effort. If success is to be achieved, cross-industry collaboration between pharma and biotechs will be critical. Biotechs possess the deep, specialised understanding of the disease biology in the relevant indications. Conversely, instances where underlying science is overruled by strategy, purely driven by generating the next blockbuster in the largest indications, regardless of understanding, will more likely be met with failure. While there may be great rewards in diseases such as Alzheimer's disease (AD), a strategy that involves throwing everything at a certain indication in the hope something will stick represents what we see as an out-of-date and costly approach.

Advancements in CNS continue to rely on highly focused and specialised technology developed by smaller and nimbler biotech companies. Mechanisms will continue to evolve and fuel advancements in targeted treatments and therapies with more broad-based offerings within large pharma portfolios.

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Companies mentioned in this report (Edison clients in bold)

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Amgen (AMGN: NASDAQ)
AstraZeneca (AZN: LSE)
Biogen (BIIB: NASDAQ)
Bristol Myers Squibb (BMY: NYSE)
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Eli Lilly (LLY: NYSE)
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Sanofi (SNY: NASDAQ)
Takeda (TAK: NYSE)
Vertex (VRTX: NASDAQ)
Vivoryon Therapeutics (VVY: Euronext Amsterdam)

CNS splits the big pharma camp

There is concern among some of the larger pharmaceutical companies that the CNS drug discovery road remains too hard, too long and too risky. In a way, this attitude is merited as many big players have experienced first-hand the challenges and costs of CNS clinical setbacks. Some of the most notable casualties include Pfizer and Johnson & Johnson's AD drug candidate bapineuzumab, Eli Lilly's AD drug duo semagacestat and solanezumab and Biogen's monoclonal antibody cinpanemab in Parkinson's disease (PD). This has resulted in a number of pharmaceutical companies curtailing development of their CNS pipelines, instead dedicating resources to disease areas perceived to be more treatable. While some have almost entirely headed for the exit, the more prescient companies have remained dedicated and have continued to invest in CNS drug development for many years, Exhibit 1.

Exhibit 1: Big pharma in CNS development

	Enhanced pipeline (>5 candidates)	Limited pipeline (1– 4 candidates)	Fully exited (no candidates)
Large pharma			
AbbVie	■		
Amgen		■	
AstraZeneca		■	
Biogen	■		
Bristol-Myers		■	
Eli Lilly	■		
Gilead			■
GlaxoSmithKline			■
Johnson & Johnson	■		
Merck		■	
Novartis	■		
Novo Nordisk		■	
Pfizer			■
Regeneron		■	
Roche	■		
Sanofi	■		
Takeda	■		
Vertex			■

Source: Edison Investment Research, company websites

A level of commitment from big pharma is key for the clinical progression of CNS targeting drugs. However, just like in oncology, in CNS we see the smaller biotechs leading the way, most often the origin of innovation in CNS drug discovery. Whether they have had a long-standing foot in the CNS camp or are interested in returning, we believe large cap pharmaceutical companies will eventually turn to their biotech counterparts to expand and bolster their pipelines.

Orphan indications may tempt a big pharma return

The orphan drugs (drugs treating rare diseases that affect less than 200,000 Americans) model represents a potentially lucrative growth opportunity that many drug makers are beginning to take a

heightened interest in. CNS indications that have been granted orphan status include Huntington's disease, as well as rare childhood neurological disorder Kabuki syndrome. Orphan designation brings with it certain benefits, including extended market exclusivity on regulatory approval, exemption of FDA application fees and tax credits for qualified clinical trials. Perhaps most incentivising is that orphan drugs can command high price tags that may generate substantial returns from smaller numbers of patients, making overall investment more appealing. According to EvaluatePharma, orphan drug sales are estimated to account for c 20% ($273bn) of all prescription drug sales by 2026. Additionally, many new drug technologies make their opening shot in rare diseases, conditions often genetically defined, and provide a platform to demonstrate clinical proof of concept. This may be followed by potential expansion into new indications. An example is Merck's blockbuster checkpoint inhibitor pembrolizumab (Keytruda, US$17.2bn sales in 2021). It received its first approval as an orphan therapy in 2014 and now dominates the immunotherapeutic market, having since received FDA approval for the treatment of 19 cancer types across c 30 indications. Those drugs showing signs of being successful orphan therapies in neuroscience may therefore pave the way for deal opportunities and entice future partners.

Out with the old, in with the new targets

The majority of CNS drugs on the market work by treating the symptoms of neurological conditions. Approved symptomatic treatments have primarily come in the form of drugs that target the 5-HT_2 serotonin and D_2 dopamine receptors, tackling conditions such as schizophrenia, depression, bipolar disorder and PD. While a number of these have been highly successful, the market is awash with 'me-too drugs', with c 150 combined 5-HT_2 and D_2 approved antagonists. Today, the focus of much CNS clinical research for neurodegenerative indications lies in developing therapies that target the underlying cause of the disease (disease modifying therapies), not just the symptoms. This has led to the identification of new drug targets and clinical investigations into therapies with novel mechanisms of action.

Genetics and precision medicine

CNS disorders often have complex disease pathologies in which there may be multiple different underlying causes that could trigger the disease. Understanding and correctly diagnosing the exact disease mechanism at play is a major challenge for clinicians. For example, there may be multiple different pathways that lead to an AD or a schizophrenic brain. However, diseases that are known to be caused by just a single genetic abnormality (monogenic) may be easier to target and carry less risk, which are appealing features for any neuroscience programme. A promising strategy that may lend itself to the treatment of such CNS disorders lies in developing drugs capable of modulating gene expression. The greatest success in treating monogenic disorders has so far been achieved in spinal muscular atrophy (SMA), a neurological genetic condition that destroys nerve cells leading to muscle weakness and atrophy. The disease is characterised by mutations in the SMN1 gene leading to a deficiency of survival motor neuron (SMN) protein, essential for nerve cell survival. Since 2016, the FDA has approved three therapies for SMA, each aimed at restoring SMN production, Exhibit 2.

A similar approach has been taken in attempting to tackle Huntington's disease (HD); however, there are currently no marketed disease modifying treatments for the condition. HD is an indication that Roche and its partner Ionis have targeted with their lead HTT gene targeting antisense therapy, Tominersen. The drug had shown signs of promise in earlier studies, but failed to show efficacy in a pivotal Phase III trial. Roche has since reignited the programme and is now planning a Phase II trial in younger adult patients, a sub-population that appeared to show signs of benefiting from treatment.

Exhibit 2: Selected CNS drugs with monogenic targets

Company	Drug	CNS indication	Defective gene	Drug type	Mechanism	Clinical status
Biogen	Spinraza	Spinal muscular atrophy	SMN1	Antisense oligonucleotide	Increases the splicing efficiency of SMN2 pre-mRNA, promoting enhanced levels of SMN protein production	FDA approved (2016)
Novartis	Zolgensma	Spinal muscular atrophy	SMN1	Adeno-associated virus (AAV) 9-based gene therapy	Delivers a copy of the SMN1 gene to enhance production of SMN protein	FDA approved (2019)
Roche/Genentech	Evrysdi	Spinal muscular atrophy	SMN1	Small molecule	Increases the splicing efficiency of SMN2 pre-mRNA, promoting enhanced levels of SMN protein production	FDA approved (2020)
Roche/Ionis Pharmaceuticals	Tominersen	Huntington's disease	HTT	Antisense oligonucleotide	Binds to mRNA, inhibiting production of toxic mutant huntingtin (mHTT)	Phase II
Oryzon Genomics	Vafidemstat	Kabuki syndrome (orphan)	KMT2D (up to 80% of cases)	Small molecule	Inhibition of lysine specific demethylase 1 (LSD1), an epigenetic modulator involved in controlling gene expression through histone demethylation	Phase Ib/II

Source: Edison Investment Research, company websites

An additional clinical approach worth highlighting is Oryzon's Phase I/II HOPE study investigating its epigenetic modulator vafidemstat, for the treatment of Kabuki syndrome. Kabuki syndrome is a rare congenital disorder (present at birth) primarily caused by a mutation in the KMT2D gene. The normal function of this gene plays an important role in brain development. The HOPE trial is planning to begin patient recruitment in H123 and is noteworthy because it combines a number of unique features that characterise interesting CNS programmes, in our view, including:

- targeting a CNS orphan indication (Kabuki syndrome), with currently no clinical competitors,
- applying a precision medicine approach in CNS with an understanding of disease pathology,
- targeting a monogenic CNS disease indication, and
- addressing a novel drug target in CNS, lysine-specific demethylase 1 (LSD1).

Few companies are investigating disease modifying approaches in CNS orphan indications (to our knowledge).

We intend to monitor the clinical progression of vafidemstat in this rare disease closely because positive readouts from the study, if achieved, may set an encouraging precedent in new approaches to monogenic CNS diseases. Oryzon is also exploring its lead CNS asset, vafidemstat, for the treatment of schizophrenia and borderline personality disorder in two ongoing Phase II studies.

Alzheimer's: Biomarkers suggest a strategic rethink

Biomarkers are biological indicators, such as proteins, used to assess the risk or presence of a disease. In drug development they are critical in confirming diagnoses, choosing the most appropriate treatment path, monitoring disease progression and measuring whether a drug modality has meaningfully engaged the desired target of interest. Clinical trials must be carefully designed by considering various biomarkers, from those that guide identification of the correct study participants through to those that can demonstrate target engagement.

The challenge in AD is that there are a limited number of biomarkers available and those that do exist may not necessarily translate into clinical efficacy; that is, treating the biomarker may not necessarily treat the disease. AD is perhaps the indication in which this has been most exemplified. β-amyloid, tau proteins and neurodegeneration are considered the hallmark biomarkers for AD. β-amyloid and tau are involved in the formation of β-amyloid plaques and tau tangles, respectively, both of which are thought to play a major role in the progression of AD. They have therefore been considered as logical targets for disease modifying therapies. However, many clinical programmes have focused purely on developing drugs targeting β-amyloid in patients with early-stage AD and

mild cognitive impairment (MCI), Exhibit 3. While these AD clinical programmes demonstrated encouraging proof of mechanism by modulating β-amyloid in earlier phases, many β-amyloid therapies have failed to show functional improvement for patients in Phase III studies. However, it appears as though the nature of the β-amyloid targeted by such therapies plays a critical role in efficacy, as evidenced by encouraging Phase III results recently reported by Biogen for lecanemab, targeting less mature β-amyloid protofibrils (aggregates).

Exhibit 3: Selected anti-amyloid β AD drugs

Company	Drug	Therapeutic purpose	Biomarker observation in earlier studies	Outcome of Phase III studies
Eli Lilly	Donanemab	Remove β-amyloid plaques	In Phase II study reduced levels of β-amyloid plaques and tau	Expected H123
Biogen/Eisai	Lecanemab	Targets less mature Aβ protofibrils	In Phase IIb study decreased levels of β-amyloid protein and reduced levels of p-tau	Statistically significant reduction in cognitive decline by 27%
Biogen	Aduhelm (Aducanumab)	Remove β-amyloid plaques	In a Phase Ib study reduced levels of β-amyloid plaques	Granted FDA approval in 2021 despite inconclusive clinical efficacy
Eli-Lilly	Semagacestat	Reduce β-amyloid production	In a Phase II study reduced levels of plasma β-amyloid protein	Failed Phase III efficacy
Johnson & Johnson/Pfizer	Bapineuzumab	Remove β-amyloid plaques	In a Phase II study reduced levels of plasma β-amyloid plaque	Failed Phase III efficacy
AstraZeneca	Lanabecestat	Reduce β-amyloid production	In a Phase I study reduced levels of β-amyloid in cerebrospinal fluid (CSF)	Failed Phase III efficacy
Merck	Verubecestat	Reduce β-amyloid production	In a Phase I study reduced levels of β-amyloid in cerebrospinal fluid (CSF)	Failed Phase III efficacy

Source: Edison Investment Research, company websites

Recruiting the correct patient trial population that is most likely to benefit from the drug is key and, in our opinion, this may have been a major contributing factor to the failure of early clinical anti-amyloid β (anti-Aβ) investigations. Around 20% of patients diagnosed with AD related dementia included in such trials did not show an increased β-amyloid profile in the brain. This result is further corroborated by a recent study from Janssen published in September 2022 investigating patient anti-Aβ treatment eligibility following AD-related MCI or AD dementia diagnosis. The study used FDA anti-Aβ treatment recommendations published following the approval of Aduhelm and found less than 30% of patients with AD MCI or AD dementia had a biomarker profile making them eligible for anti-Aβ treatment. This gives credence to the need for more sophisticated diagnostic AD screening methods and new therapies, addressing new targets with new mechanisms of action, in our view.

Vivoryon Therapeutics is a German biotech attempting to identify new AD treatments with its lead candidate varoglutamstat, a small molecule inhibitor that aims to target multiple hallmarks of AD. Varoglutamstat's key differentiation from AD therapies that purely focus on β-amyloid plaque removal, such as Aduhelm, is its dual mechanism of action, targeting two critical enzymes further upstream in AD pathogenesis (QPCT and QPCTL). Inhibition of both QPCT and QPCTL is believed to prevent the formation of a toxic β-amyloid variant (Aβ-N3pE), a precursor to β-amyloid plaques, and CCL2, a protein found to play an important role in tau pathology and neuroinflammation, thereby addressing multiple AD pathways. The drug is currently progressing in two key Phase II studies in the EU and United States.

Actinogen Medical is an Australian biotech with an approach that is also differentiated from classic anti-Aβ antibodies and is focusing mainly on cognitive enhancement (rather than disease modification). To our knowledge, the company's lead asset, Xanamem, is the only inhibitor in clinical development to treat cognitive impairment that is targeting 11β-HSD1, an enzyme generating excess cortisol in AD patients resulting in disease worsening. Having previously demonstrated the beneficial effects of Xanamem on working memory in healthy patients, Actinogen will begin recruiting tau biomarker confirmed early AD patients with MCI into its follow-on Phase IIb XanaMIA in H123. For more details on Actinogen's clinical development plans, please see our recent initiation.

The development of technologies to identify new targets in the fight against AD has prompted what may be considered a return by Merck, which has recently entered a strategic collaboration with Cerevance. Cerevance is a private biotech with a nuclear enriched transcript sort sequencing (NETSseq) platform that provides the ability to measure low levels of protein targets in diseased brain cells that may play a critical role in AD pathology. At low levels of expression, these potential therapeutic targets would otherwise remain undetected using conventional sequencing methods.

Aduhelm controversy paves the way

The FDA's approval of Biogen and Eisai's Aduhelm (Aducanumab) in 2021 marked what may have initially been perceived as the clinical eureka moment in the development of new drugs to tackle AD. Not only was it the first therapy to be approved for the condition in roughly 20 years, but it was the first to be approved with a disease modifying mechanism of action. Unfortunately, Aduhelm is now regarded as one of the most controversial approval decisions made by the FDA.

In 2019 Biogen decided to discontinue two pivotal Phase III trials for Aduhelm in patients with early stage AD after it concluded the studies would not meet their primary endpoint of efficacy. However, following additional analysis of the Phase III trial data, which the company indicated showed that drug is pharmacologically and clinically active, Biogen pursued regulatory approval for the drug later that year. The FDA approved Aduhelm using the accelerated approval pathway, which can be based on a surrogate endpoint, β-amyloid plaque reduction, stating that a surrogate endpoint is 'reasonably likely to predict a clinical benefit to patients'. The controversy is that relatively little evidence existed to demonstrate targeting β-amyloid translated into clinically meaningful improvements in patients. In essence, there is a perception that Aduhelm received approval without showing sufficient clinical benefit. Subsequently, Biogen has had to cut pricing for the drug by 50% to gain buy in from insurers; however, for Medicaid, coverage is limited to patients enrolled in clinical trials approved by the Centers for Medicare and Medicaid Services (CMS).

While the Aduhelm story might appear to have had a bad ending, what it has done is help create an impression of regulatory feasibility for new AD treatments. Indeed, the β-amyloid hypothesis has been revived following positive readouts from Eisai and Biogen's Phase III study of β-amyloid targeting lecanemab, slowing disease progression in patients with mild AD by 27% versus placebo; however, we will still need to see whether or not this benefit ultimately translates into clinical practice and broader CMS reimbursement. In the meantime, the news provides a welcoming boost for Eli Lilly and Roche's β-amyloid's donanemab and gantenerumab, respectively, but also for the next generation of disease modifying AD therapies. Notably, the FDA has agreed to an expedited review process for donanemab, with a potential regulatory approval decision by February 2023.

Machine learning: A predecessor to the clinic

The concept of machine learning in drug discovery has certainly generated much hype in recent years. The idea of harnessing big data and complex quantum computing algorithms to expedite drug discovery, on the face of it, sounds appealing. However, for many investors, the concept of 'machine learning' is akin to that of a black box, with only a handful of people, often the designers, truly understanding its inner workings. The biggest question is whether machine learning actually delivers clinical candidates. The answer, according to Swedish biotech IRLAB Therapeutics's proprietary Integrative Screening Process (ISP) research platform, appears to be yes.

IRLAB's ISP platform is at the heart of its drug discovery engine, enabling the discovery of new drugs for CNS-related diseases. In its simplest form, the ISP platform is a database containing a wealth of biological, chemical and safety data related to a compound's impact on a biological system, such as an animal model. The platform contains a growing database of almost 1,400 CNS drug-like compounds developed over 25 years. By drawing comparisons between these compound

datasets, the machine learning tool can guide and expedite the design of future drug candidates at an earlier stage using an evidence-based modelling approach. This allows IRLAB to focus on the development of those molecules predicted to have the best properties with potentially lower risk and a greater probability of success. While many biotech and pharmaceutical companies have developed screening platforms, the ISP platform is unique in combining measurements of both neurochemistry and behaviour in living organisms using machine learning analytics. Importantly, this has translated into clinical candidates and, since 2000, IRLAB has leveraged the ISP platform to progress eight drug candidates into clinical studies. Today, the company's pipeline consists of two-Phase II clinical assets and a further two expected to enter the clinic in 2023.

Leapfrogging the blood-brain barrier

Clinical investigators continue to make steps in developing the next generation of leading pharmaceutical products; however, there is a risk that the true therapeutic potential of many CNS drugs goes unrealised. This is largely due to the inability to deliver them to their site of action in the body, particularly CNS diseases, which require drugs to target the brain. Targeted delivery to the brain is extremely challenging with c 98% of newly discovered small molecule drugs unable to cross the blood-brain barrier (BBB). With the evolution of more sophisticated CNS therapies, such as cell and gene therapies, we feel there is a continued need to develop new technologies that transport efficacious drugs into the brain safely.

ReNeuron Group is a UK-based stem cell research company focused on the development of exosomes, a new drug delivery platform that aims to address the challenges of the BBB. Exosomes are small, membrane bound compartments naturally produced by all cells in the body and act as transporters of materials between cells. They can be thought of more simply as cellular couriers. ReNeuron's approach is to harness the natural cellular targeting ability of exosomes and engineer them to incorporate a therapeutic agent. The drug modality of choice has potential to be small molecules, proteins, gene therapies and RNA therapies. The company has reported encouraging preclinical data demonstrating that its exosome platform can deliver drugs to specific areas in the brain. Additionally, ReNeuron has recently shown its exosomes can effectively deliver siRNA, a new class of complex drug modality in which targeted drug delivery is a significant challenge, to brain cells. The pipeline of RNA therapeutics is poised to deliver future drug candidates in CNS and ReNeuron may be uniquely positioned to target this future market.

CNS trials need clinically meaningful results

Together with ineffective drugs and inadequate target selection, poor clinical trial design has played a role in the failures of CNS trials, from suboptimal patient recruitment to inappropriate endpoint selection. The difficulty faced in selecting trial endpoints is that they must be measurable and meaningful in the context of patients. That is, they must be clinically significant, reflecting the importance of treatment regarding its impact on the patient and/or family, whether it makes a real difference to their lives, the duration of time the effect lasts, cost-effectiveness and ease of implementation. In reality, it is highly unlikely that payers will provide coverage for a drug that does not demonstrate clinical relevance. One of the common pitfalls of assessing the outcomes of clinical studies is the interpretation of the word 'significance' and the misinterpretation that 'statistical significance' is the same or translates into 'clinical significance'. A trial may report drug survival results of 6.25 months versus 5.91 months (P = 0.041), meaning there is only a 4.1% chance the difference between the groups occurred by chance and therefore it is statistically significant. However, the clinical relevance of this is a mere 10-day improvement in survival, which many would argue is not meaningful.

In our opinion, optimal trials are those designed to include multiple endpoints that demonstrate efficacy in a number of meaningful ways, such as favourable changes in symptoms, function and biology that provide clear readouts right upfront and clinical timescales that allow longer-term assessments of the impact of treatment on patients. CNS trial designs are incredibly complex, and nobody has a magic bullet for the perfect study. Importantly, while drugs will most likely get approved based on statistical significance, uptake in clinical practice and reimbursement is ultimately dictated by the clinical relevance and effectiveness of drugs. What Aduhelm has taught us is that reimbursement coverage is critical for commercial success in high-stakes indications such as AD.

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