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# The Quiet Revolution in Central Nervous System Therapies (Part 2):

## Outlook for 2021 and Beyond

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White Paper

# The Quiet Revolution in Central Nervous System Therapies (Part 2): Outlook for 2021 and Beyond

In Part 1, we spent a great deal of time looking backward. We discussed the "quiet revolution" that has been taking place in CNS over the past several years. Interesting advances are being made in a range of CNS therapies while other areas, such as oncology, tend to get more attention. We also shared how investment activity has been building in CNS, helping to fuel those advancements.

Here, we turn our gaze forward. 2021 promises to be a big year for the broader CNS market, and we outline some of our thoughts on why we think that's the case. Developments during the year ahead are likely to have far-reaching implications, so let's jump in and see what might happen.

## Predictions for 2021 Onward: Looking at the CNS Space Through a Disease Specific-Lens

### A Word About COVID-19

2021 will be an interesting year in CNS but there is the added complexity of COVID-19. As everyone is aware, the FDA issued dramatically accelerated approvals for the current COVID-19 vaccines. As a result of those accelerated approvals, the FDA is now under greater pressure to display strength and rigor by increasing the level of scrutiny on subsequent drug approvals.

This is complicated by travel restrictions that are barring inspectors from visiting manufacturing facilities, resulting in some recent rejections due to manufacturing concerns. Some notable recent examples include:

- The FDA rejected Alkermes' schizophrenia and bipolar 1 drug (ALKS3831) due to manufacturing concerns. There were no problems with the data, but the FDA was concerned with tablet coating issues. The FDA had used remote inspections due to COVID-19 restrictions. Even though an FDA advisory panel had backed Alkermes, the agency decided to take the more conservative approach.[1]
- The FDA rejected Supernus for two applications (SPN-812 for ADHD and SPN-830 for Parkinson's disease). Although no reason was given by the FDA, Supernus voiced that it had to do with chemistry, manufacturing, and controls (CMC) issues.[2]

We expect this trend of heightened FDA scrutiny (often related to manufacturing) to continue through 2021. Given that this will tend to affect smaller companies, those companies might need to focus more resources on manufacturing or partner with larger companies that have the needed expertise already fully developed. This could lead to larger deals in areas with greater manufacturing complexity, such as gene therapies. This trend has already started in December with Eli Lilly acquiring Prevail Therapeutics.

### The CNS Market Now

#### Top Companies

- In 2019, Biogen was the CNS market leader with 10% market share, bolstered by Tecfidera (for multiple sclerosis), the leading CNS product of 2019 with $4.4 billion in sales.
- By 2022, Roche could overtake Biogen with Ocrevus (also for MS), with forecasted sales of $7.7 billion by 2025.

#### Top Products

- MS therapies held the top spot with 7 of the top 15 best-selling CNS products in 2019, with 25% of the CNS market. Biogen's Tecfidera and Roche's Ocrevus led the way.
- Antipsychotics were in second place with 13% market share.
- Antiepileptics were in third place with a 12% share.

Source: "A view into the central nervous system disorders market." *Biopharma Dealmakers*. Sept. 1, 2020

### Alzheimer's Disease

#### Amyloid Plaques

It is hard to overstate the importance of the FDA's upcoming decision on Biogen/Eisai's aducanumab. Aducanumab has had a rocky clinical trial history with Biogen originally discontinuing its development due to a statistics-based futility analysis.

After re-analyzing their clinical trial data collected at the end of phase 3 trials, Biogen decided to pursue FDA approval. In early November, an FDA advisory panel reviewed the drug and clinical trial data negatively despite the FDA being more positive about it.

Given the inconsistent data and the potentially tougher stand of the FDA, we think there's a very good chance the drug will be rejected. Moving forward, Biogen and Eisai may continue to look into aducanumab as a potential therapy for smaller sub-sections of Alzheimer's disease, focusing treatment and limiting its overall market potential. Regardless, if aducanumab fails to garner FDA approval, we think there are a couple of implications.

Predictions:

1. **Biogen will need to do more deals. Biogen recently teamed up with Sage therapeutics to develop therapies for depression in a deal potentially worth over $3B. They will jointly develop and commercialize zuranolone (SAGE-217) for major depressive disorder (MDD) and postpartum depression (PPD) as well as SAGE-324 for tremors.**[3]
2. **The amyloid hypothesis will fail, even if Biogen and Eisai continue development of their other amyloid antibody; Ban2401. For others in the field, there may be a shift to other Alzheimer's drug targets or an exit of the market altogether. Aducanumab is only the most recent miss in the amyloid field, following bapineuzumab (Pfizer and J&J) and solanezumab (Eli Lilly).**

There is hope in Alzheimer's though, as other treatment approaches are being developed. A great example of a therapy that has the potential to make an impact in Alzheimer's is masitinib by AB Science. In December of 2020, the company reported promising results from a phase IIb/III clinical trial in confirmed mild to moderate Alzheimer's disease. Masitinib is a selective oral tyrosine kinase inhibitor that is thought to act by either abating neuroinflammation or by targeting amyloid-beta signaling and tau phosphorylation through Fyn Kinase.[4]

Also in December 2020, Novo Nordisk announced plans to initiate a phase 3a program to investigate the safety and efficacy of once-daily oral semaglutide in early Alzheimer's disease. Interestingly, semaglutide (a GLP-1 receptor agonist) is an anti-diabetic medication used to treat type 2 diabetes but has been shown to have the potential to decrease the occurrence of developing dementia. If impaired insulin signaling can be found to contribute to the development of dementia, it would bolster the hypothesis that Alzheimer's disease may be "type 3 diabetes" and open a new therapeutic avenue that can be targeted to treat the disease.[5]

### Diagnostics

There is also work underway on diagnostics for Alzheimer's disease. However, the success of these tests will be dependent on the availability of an effective Alzheimer's therapy:

- For example, C2N Diagnostics has released the first blood test for Alzheimer's disease in the US, targeting patients 60 years old or older. The test is not covered by payers, costs $1,250, and has not been approved by the FDA. This is C2N's only marketed product and, without a treatment, there may be little reason for patients to use the diagnostic and learn they have the disease.[6]
- Eli Lilly has a P-Tau biomarker assay in initial development for early-stage Alzheimer's Disease. Again, one wonders if payers will cover the test if there is no effective treatment nor preventative measures available.[7]

Predictions:

1. **If aducanumab is not approved, the novel diagnostics will be less likely to be adopted and payers may find it less compelling to cover.**
2. **We will see an acceleration of alternative approaches to treat Alzheimer's focusing on metabolism (as the notion that Alzheimer's is like "type 3 diabetes" gains more traction), preventing neuronal senescence, and a stronger focus on Alzheimer's as a Tauopathy rather than (or in addition to) pathogenic amyloid beta accumulation. These will spur M&A activity and development in these new areas.**
3. **New government focus will help bolster research into Alzheimer's disease as these failures may make pharmaceutical companies more hesitant to find a cure or therapy.**

## Duchenne Muscular Dystrophy

The Duchenne muscular dystrophy (DMD) space has been getting more crowded with Solid Biosciences and Pfizer in the mix. There is now more pressure on companies like Sarepta that focus so much on DMD to bring therapies to market.

Sarepta gained approval of Exondys 51 on an open label 12-person study. If the FDA takes a tougher stand, as we speculate, it may make things difficult for Sarepta's SRP-9001. Because of COVID-19, Sarepta is proposing SRP-9001-103 (study 103), which is an

open label study in up to 10 patients to evaluate the safety and expression of SRP-9001 and accelerate Sarepta's validation of it.[8] It remains to be seen whether a tougher FDA will accept this study design. Incidentally, results from SRP-9001-102 (study 102), a double-blind placebo controlled phase 2 study of SRP-9001 with 41 patients, are expected in 2021.

Predictions:

1. Early success leveraging small clinical trials in DMD have led to the continuation of these types of studies. But, although smaller trials in the CNS space are feasible, they need to be well-designed as the FDA grows more skeptical about the data generated.
2. The FDA's response to small clinical trials—especially with adeno-associated viruses (AAV)—will set the tone for other genetic treatments and the FDA may not be as positive as before.
3. As the competition for DMD therapies is heating up, there is increased pressure for Sarepta to succeed in developing SRP-9001. If this fails, they may lose their foothold in the market to Pfizer and/or Solid Biosciences, affecting Sarepta's overall success and valuation.

## Psychiatric Disorders

The psychiatric illness space has some important readouts coming in 2021. It will be a "make or break" year for some. There is interesting movement in traditional areas of therapy for mental illness, as well as with therapies that are considered more "taboo" such as ketamine-based treatments like Spravato and others.

COMPASS Pathways' COMP360, a synthetic derivative of psilocybin (the active ingredient in "magic mushrooms") is intended to help patients with treatment-resistant depression. It's in Phase 2b clinical trials, which should end in December 2021. COMPASS Pathways has been successful in raising money to fund its research, including interest from Otsuka.[9]

In 2018, COMP360 gained breakthrough designation by the FDA.[10] Its success or failure will help set the tone for "taboo" drugs moving forward. Already, clinical trial successes of psychedelic treatments has led to the launch of investment funds like Neo Kuma Ventures which is completely dedicated to psychedelic healthcare investment and is the first of its kind in Britain.[11]

More traditional treatments have also seen recent successes. For example, in March of 2019, Sage Therapeutics' Zulresso was approved. It is a GABAA agonist for women with postpartum depression. The IV medication costs about $34,000 per treatment course that has been shown to be effective for up to 30-days.

Predictions:

1. We will see continued investment growth in treatments for psychiatric disorders, with resources going into both "taboo" treatments, like those to be funded by Neo Kuma Ventures, and more traditional medications (albeit with newer treatment paradigms and different mechanisms of action in many cases).
2. Smaller companies that are heavily invested in CNS could sink or swim during 2021. Some examples include:
   a. Axsome Therapeutics, in addition to recent success in phase 3 clinical trials for AXS-07 for treatment of acute migraine[12], shows positive long-term results in major depressive disorder (MDD) from its phase 3 trial of AXS-05 (an experimental non-competitive NMDA antagonist). The NDA for both AXS-05 and AXS-07 are expected in the first quarter of 2021.[13]
   b. ACADIA pharmaceuticals has submitted an NDA for Nuplazid (already approved for Parkinson's disease psychosis) for dementia-related psychosis. The expected PDUFA date is April 3, 2021.[14]
   c. Cerevance's CVN058, a small molecule therapy for cognitive impairment associated with Schizophrenia (CIAS), may move into a phase 2 study next year. If approved, it will be the first therapy to treat CIAS in Schizophrenia.[15]
   d. In November, Praxis had a clinical hold imposed for its lead MDD therapy. A week later, Praxis announced it has a path to lifting the hold. The necessary animal tox studies should be completed in the first quarter of 2021 with a phase 2/3 study in MDD starting in the first half of 2021.[16]
3. The use of digital therapeutics supporting psychiatric disorders will continue to grow. This is driven in part by the COVID-19 pandemic, which simultaneously increases the need for support and drives patients to more digital interactions.

## Pain

Given the much-publicized opioid crisis in the US, it's no surprise that most of the action in this space will focus on either non-opioid treatments for pain or therapies for opioid use dependency (OUD).

### Non-Opioid Treatments for Pain

Two high-profile monoclonal antibodies serving as nerve growth factor (NGF) inhibitors have important milestones in early 2021. The NGF drug class itself has been shelved for nearly a decade due to skeletal side effects but the opioid crisis pushed the FDA to lift its five-year clinical hold in 2015.

One NGF therapy being developed is tanezumab, a joint effort by Eli Lilly and Pfizer. In March 2020, the FDA accepted a Biologics License Application (BLA) for subcutaneous use of 2.5 mg tanezumab in patients with chronic pain due to moderate-to-severe osteoarthritis with inadequate pain relief with other analgesics. The PDUFA date is December 2020.[17] Tanezumab has not been without controversy, however as Tanezumab-treated patients have experienced more joint safety events and total joint replacements than those treated with placebo.[18]

The other NGF therapy, fasinumab, is being brought to market through partnership between Teva Pharmaceuticals and Regeneron. Phase 3 results showed that 1mg fasinumab induced statistically significant improvement in the measurement of pain and physical function among osteoarthritis patients. However, there are joint issues associated with fasinumab, as well. This has caused the developers to convert a phase 3 trial to a long-term safety study.[19]

Another interesting situation involves Trevena. That company received approval for OLINVYK in August of 2020. OLINVYK targets the Mu opioid receptor. Trevena hopes to address problems with opioid abuse by limiting OLINVYK use to short-term IV administration in hospitals or other controlled clinical settings.[20] Data from 2021 will tell if OLINVYK will be widely adopted and if it will help stem the potential for opioid abuse which, if successful, will cause others to follow in their example.

### Government interest in OUD

Related to the fight against OUD, BioXcel Therapeutics announced a grant by the US Department of Defense (DOD) for BXCL501 for PTSD related to alcohol and substance abuse disorder (ASUD). BXCL501 is an orally dissolving film formulation of dexmedetomidine (dex) in late stage development for agitation and opioid withdrawal symptoms.

Prediction:

1. **We will see continued investment growth related to:**
   a. **Non-opioid treatments for pain.**
   b. **Treatments for opioid use dependency.**

## Gene Therapies

In 2006, Dr. Shinya Yamanaka and his team discovered a method to reprogram mature cells to become pluripotent, which means they can give rise to multiple different cell types. This finding led to the establishment of induced Pluripotent Stem Cells (iPSC) and his Nobel Prize in 2012.[21]

With its discovery, the scientific community was elated to find an alternative to embryonic stem cells (ESC). However, 14 years since, there are still no iPSC therapies approved in the US. The scientific community is coming to grips with the shortcomings of iPSC technology as a treatment including cost of production, genomic instability of the cells, and the potential for immunogenicity.[22] As such, the initial promise of personalized medicine heralded by the discovery of iPSC has been tampered down, at least until these shortcomings are solved.

Similarly, gene therapies have held a lot of initial promise and which may be tested in 2021. In recent years, large pharmaceutical companies have been advancing in the gene therapy space, working to bolster their capabilities. During 2021, we will see how successful many of these efforts will be. If things work out well for these larger companies, it may encourage others to follow their leads. Some notable examples include:

- UCB acquired Handl Therapeutics, which focuses on AAV-based gene therapies for neurodegenerative disease. UCB has also partnered with Lacerta Therapeutics to study AAV-based therapies for CNS diseases with high unmet needs.
- Bayer is working on gene therapies, stem cell therapies, gene augmentation, gene editing and allogeneic cell therapies. They acquired AskBio and BlueRock therapeutics in 2019 for $600M. AskBio has signed deals with Pfizer in DMD. BlueRock has its own Parkinson's program to regenerate lost dopamine-producing cells.
- In December 2020, Eli Lilly bought Prevail, a neurodegenerative disease player, for $1.04 billion to help reinforce its early-stage pipeline.[23] Prevail has AAV9 therapies in the pipeline, both in phase 1/2: 1.) PR001 is targeted towards Parkinson's disease with GBA1 mutations and neuropathic Gaucher disease (nGD); 2.) PR006 is a single-dose AAV9 for patients with frontotemporal dementia with GRN mutations (FTD-GRN).

Although big moves have already occurred in this space, there are still many smaller biotech companies focused on CNS and have found success in garnering funding. A prime example of this is Taysha Gene Therapies. Recently launched, in April of 2020, Taysha raised $95 million in series B funding in July, had a $100M

IPO in September, and plans to invest $75 million to build a commercial-scale manufacturing facility in North Carolina. All of this was achieved with a lead program that was just recently cleared by Health Canada for phase 1/2 clinical trials in infantile GM2 gangliosidosis.[24]

Predictions:

1. Several big pharmaceutical company players will initiate investigation into gene therapies, shifting the spotlight away from the smaller biotech firms that have been largely running the show.
2. Early successes will lead to new or continued investment into smaller biotech companies like Taysha Gene Therapies as the pharmaceutical industry realizes the current and near-future potential of the field of gene therapy.

## Some General / Additional Predictions

### Companies Looking to Invest

- **Biogen** – Given the situation with aducanumab, coupled with the genericization of its main revenue driver Tecfidera, investment activity will be extremely important to Biogen and could have a strong impact on how the company moves forward. It needs to address potential revenue shortfalls but quick fixes can be found, just like the recent move to partner with Sage Therapeutics.
- **Amgen** – Amgen will look to build upon its migraine portfolio, driven by Aimovig, a calcitonin gene-related peptide (CGRP) antagonist.
- **J&J** – J&J has developed a robust portfolio of drugs that can be further complemented in CNS.
- **Novartis** – Novartis will continue to expand its CNS portfolio.
- **Otsuka** – Otsuka will move to further bolster its CNS pipeline.
- **Eli Lilly** – The recent acquisition of Prevail (see above) makes big investments from Eli Lilly a little more unlikely but, historical strength in CNS and recent deals may look to grow even more in this area.
- **UCB** – UCB will make investment moves to further diversify its portfolio away from epilepsy.

### Spaces That Will Be More Active for Business Development and Licensing

In 2021, we expect the CNS space to continue to grow overall, but we think there will be higher activity in the sub-spaces below.

#### Psychiatric Illnesses/Mental Health

The recent substantial activity in mental health in both previously 'taboo' and traditional medication is expected to continue into 2021. This market has a distinct need for new therapies and our understanding of the brain is reaching a point where help can be delivered. Axome Therapeutics, with its clinical trial success in MDD (and also acute migraine treatment) is one company to watch.

#### Neuromuscular Disease

With the recent advances in gene therapy, there has been increasing interest in treating neuromuscular diseases with defined genetic origins (e.g., DMD). Larger pharmaceutical companies will continue to shore up expertise neuromuscular disease-related treatment

Outside of gene therapy, there has been movement in treatments towards myasthenia gravis using antibody treatments. Two companies to watch are:

- Viela Bio with inebilizumab, initiating a phase 3 pivotal clinical trial in 2020[25]
- Argenx with efgartigimod, with plans to submit a BLA in 2021 following positive top-line phase 3 clinical trial results[26]

#### Genome Engineering

Business development and licensing in genome engineering has been running hot with major deals struck by Bayer, UCB, and Eli Lilly. As the promise of genome engineering bears out, there will be continued deals made focusing on AAVs and other platform technologies that enable gene therapy. Companies to watch include Precision Bio, BioXcel, Neuron23, LocanoBio, and Neurogene.

#### Novel Approaches to CNS

In 2020, we saw novel approaches to treating CNS diseases and we expect that these will continue in 2021. Keep an eye on the companies below.

- Rubedo Life Sciences is advancing therapies towards neurodegenerative conditions, age-related diseases, and muscle disorders. Interestingly, Rubedo developed the ALEMBIC drug discovery platform that identifies therapeutic candidates against senescent cells, pro-inflammatory, and profibrotic cells.

- Apple Tree Partners is funding the development of Nereid Therapeutics with $50 million to study biomolecular condensates as a new platform to develop treatments for neurodegenerative diseases like ALS, Alzheimer's, and Huntington's disease.[27] Successful therapies coming from the study of biomolecular condensates would bolster this platform as a viable method to develop CNS drugs.
- Clene Nanomedicine is developing bioenergetic nanotherapeutics. Particularly, CNM-Au8 is an add-on treatment for neurodegenerative diseases (Parkinson's, ALS, MS). Pre-clinical models showed re-myelination and neuroprotection capabilities of CNM-Au8. Interim results of CNM-Au8 in phase 2 clinical trials (REPAIR-MS, REPAIR-PD) showed positive results in both MS and Parkinson's disease with bioenergetic improvements in NAD and ATP levels.[28] In September of 2020, Clene Nanomedicine announced plans to go public through a merger with Tottenham Acquisition.[29]
- Trevard Biosciences is partnered with Zogenix to develop RNA-based therapies to treat Dravet syndrome and other genetic epilepsies. Their aim is to use mRNA stabilization to increase expression of the healthy copy of SCN1A (the gene associated with Dravet syndrome) and codon suppression.[30] As mentioned above, epilepsy's market share comes in 3rd in the CNS market, meaning that success in this partnership can lead to strong interest from other pharmaceutical companies.

Clearly, the CNS market offers much to track in 2021. The "Quiet Revolution" continues, and we will be sure to keep any eye on developments, offering insights for the biopharma innovators that are operating in this space.

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