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Parkinson's Disease: Ripe For A Rethink

Developments In A Burgeoning Market

by Jo Shorthouse

Despite decades of R&D, there are no disease modifying therapies on the market for Parkinson's disease, and few efficacious products for non-motor symptoms. Clinical setbacks have been rife but breakthroughs in diagnostics and a better understanding of disease pathology brings hope for the future. In Vivo speaks to some of those responsible for bringing innovation to the field.

Parkinson's disease affects over 10 million people, a huge market that has no disease modifying treatments. Our aging population will catalyze this unmet need, and Datamonitor Healthcare forecasts the number of prevalent cases of PD to increase by 30.8% worldwide between 2018 and 2027.

By 2031, the market in the US, Japan and the five major EU markets is forecast to reach just over $6bn. Standards of care have been established by well-known brands used in clinical practice for many years. Products that physicians are familiar with, such as Levodopa products, continue to hold a significant market share.

While the number of patients is growing, in parallel so is the level of investment and underlying knowledge connected with this debilitating disease.

Key Takeaways

- By 2031, the Parkinson's disease market in the US, Japan and five major EU markets is forecast to reach just over $6bn.
- While there have been 18 approvals by the FDA in the past eight years for PD treatments, the advent of discoveries in genetics and more understanding about the biology of the disease has spurred

Blessed And Cursed

"Parkinson's disease is blessed and cursed," Mark Frasier, chief scientific officer at the Michael J Fox Foundation, told *In Vivo*. "It is blessed in the sense that there are a number of approved treatments and very effective treatments for Parkinson's," he said. However, "because of the effective treatments, historically there has been a lower incentive to invest in Parkinson's therapeutic development, because there are commercially available treatments," he said.

investment in modifying treatments or against targets that could slow or stop the progression of Parkinson's.

- Despite recent clinical trial failures, the PD pipeline is progressing. There is vast diversity in molecular, genetic and inflammation targets, but also in therapeutic approaches being tested in the clinic.

There have been 18 new approvals by the FDA in the past eight years, giving neurologists an increasing number of tools at their disposal to mitigate the condition. However, the advent of discoveries in genetics and more understanding about the biology of PD has spurred investment in disease modifying treatments or against targets that could slow or stop the progression of Parkinson's.

In The Clinic

Anyone with even a casual interest in the news flow coming from the neuroscience research field will have noticed a trend of clinical failures in PD recently. Just this year, the industry has seen Neuraly, Inc.'s lead candidate fail a Phase II trial in early PD, Aptinyx faced yet another clinical setback as its Phase II candidate failed to improve cognitive impairment in patients, and Irlab Therapeutics AB's first-in-class therapy dopamine D3-receptor antagonist, mesdopetam, missed its primary goal in a mid-stage study. (Also see "*Path Ahead For Neuraly's NLY01 Unclear After Phase II Parkinson's Disappointment*" - Scrip, 28 Mar, 2023.) (Also see "*Aptinyx Pulls Back From Neuropsychiatry After Mid-Stage PD Failure*" - Scrip, 1 Mar, 2023.) (Also see "*Irlab Parkinson's Pact With Ipsen Up In The Air*" - Scrip, 18 Jan, 2023.)

Talking to *In Vivo* about the clinical hiccough, Irlab board member Gunnar Olsson, explained that "up until you start your Phase III trial, you're just gathering information so that you can make decisions about how best to design your Phase III program. I think that we're in a very good position." Mesdopetam is being studied for levodopa-induced dyskinesia, involuntary movements that can occur after prolonged treatment with levodopa.

Olsson points to Lecanemab's Phase IIb failure as an example of a drug that can fail earlier in its clinical journey and continue to be a successful drug. (Lecanemab, sold as Leqembi, is a monoclonal antibody medication used for the treatment of

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Alzheimer's disease.) In Irlab's case, its researchers were encouraged on the secondary endpoint of its unified dyskinesia rating scale (UDysRS) score. This showed that the drug significantly reduced dyskinesia as early as week 4 at the 7.5mg twice-daily dose.

Olsson said that mesdopetam, a once daily oral drug, can be given up to the intended dose 7.5mg without being limited by side effect profile. Supernus' Gocovri (amantadine) is the current standard of care for dyskinesia. "Most patients are undertreated. If they have amantadine it's not driven to the dose level, where there is an effect," said Olsson.

A Diverse Pipeline

While mesdopetam's Phase III trial design is still under wraps, and other setbacks and timelines have disappointed observers of the field, there is still progress in this market that could amount to 12.4 million prevalent cases by 2027 according to Datamonitor Healthcare. "It's the most robust pipeline and most diverse pipeline of different programs in clinical trials we've ever seen," said MJFF's Frasier, adding that is diversity in molecular, genetic and inflammation targets, but also a diversity in therapeutic approaches currently seen in the clinic.

The MJFF is currently tracking 146 different clinical approaches or therapeutic approaches in the global pipeline. "As someone who has been in the field for over 20 years, I am pleased with the amount of innovation and the different strategies that are being deployed to Parkinson's. It's an exciting time," said Frasier.

According to Datamonitor Healthcare, the overall likelihood of approval (LOA) of a Phase I PD asset is 11.3%, while a Phase III asset's LOA is 71.4%. Therapeutics in this space, on average, take 13.1 years from Phase I to approval, compared to 10.3 years in the overall neurology space.

Welcome success came in January when NeuroDerm Ltd, owned by Mitsubishi Tanabe Pharma Corporation, announced that its Phase III study of ND0612 – a continuous, 24-hour subcutaneous infusion of liquid levodopa/carbodopa (LD/CD) – met its

NeuroDerm Parkinson's Drug Inches Closer To Market With Phase III Win

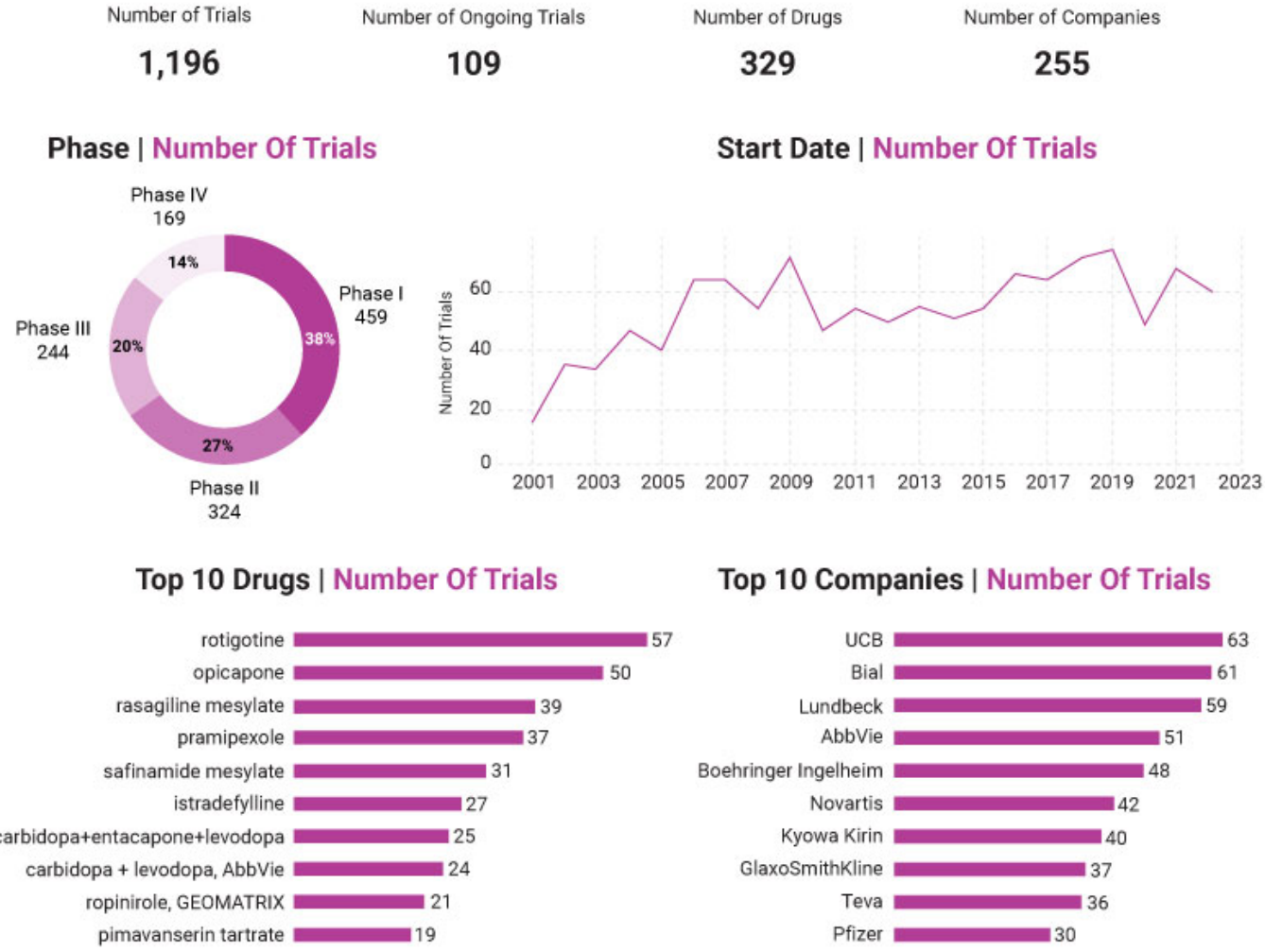
By Alaric DeArment

09 Jan 2023 Mitsubishi Tanabe Pharma paid $1.1bn to acquire the Israeli biotech in 2017 for a drug that analysts forecast to represent a market opportunity worth up to $1.7bn in peak sales. *Read the full article here*

primary endpoint of "on" time without dyskinesia along with positive and clinically meaningful results for the key secondary endpoint of "off" time. Add to this Phase II success from Cerevance's CVN424, and with more assets entering Phase II from other companies the picture is not so bleak. (Also see "*NeuroDerm Parkinson's Drug Inches Closer To Market With Phase III Win*" - Scrip, 9 Jan, 2023.)

Data from Citeline's TrialTrove indicate that there are a total of 1,196 trials ongoing in PD, 329 drugs in the clinic, and 255 companies involved in the space (*see Exhibit 1*).

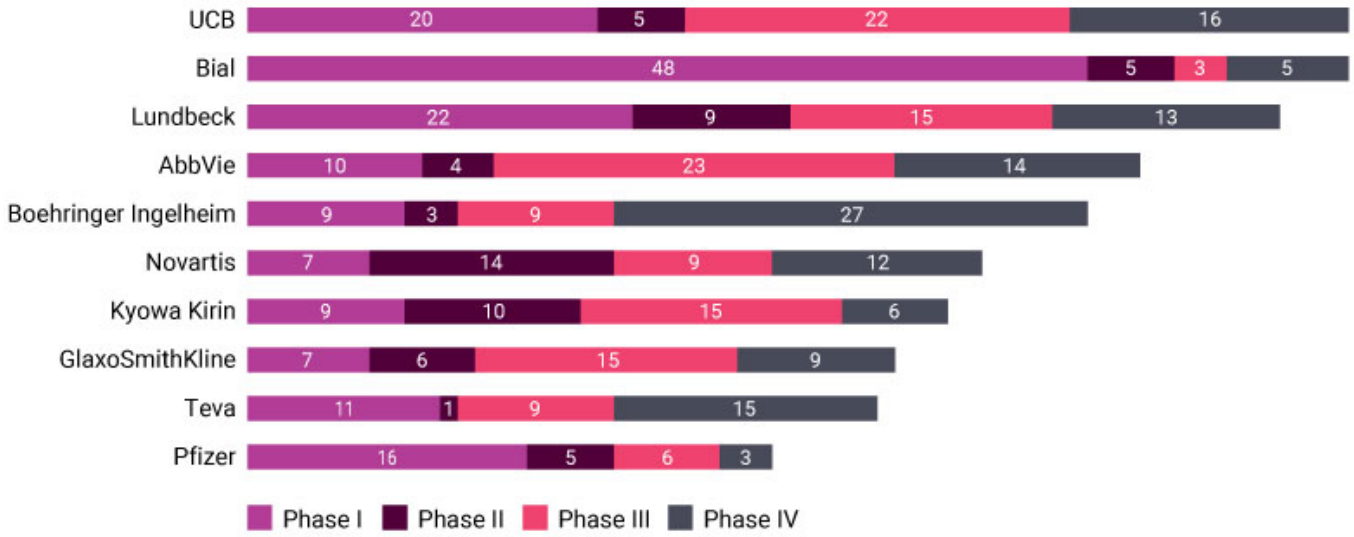
A snapshot of Phase I-IV clinical trials for primary investigational drugs with at least one industry sponsor in the Parkinson's disease space in the curated Trialtrove database. **In the last 20 years, Parkinson's disease trial starts reached their highest point around 2019.** *Phase I/II and Phase II/III trials are counted as Phase II and Phase III, respectively.*



Belgian pharma company UCB tops the list of industry sponsors with the most trials, numbering 54 completed trials, with four currently ongoing (*see Exhibit 2*). Martin Citron, head of research Belgium, UCB, told *In Vivo* that its approach is to "go broad and deep and start out with understanding what the unmet patient needs are." In contrast to Alzheimer's disease, PD has "pretty decent" treatment for motor symptoms with a "huge need" in non-motor symptoms.

A snapshot of Phase I-IV clinical trials for primary investigational drugs with at least one industry sponsor in the Parkinson's disease space in the curated Trialtrove database. **AbbVie has the highest number of Phase III Parkinson's disease industry-sponsored trials, while Bial has completed by far the most Phase I studies.**

Top 10 Comapnies | **Phase** | Number Of Trials



"That's an area that we're pursuing for symptomatology because we think there's still quite a bit of space there. And when we talk to patients, that's one of the main things they raise," Citron said. The Brussels-based company interviews patients that use its Neupro patch (rotigotine transdermal system). Input received from patients infer that non-motor symptoms such as pain, sleep disturbances, mood disorders, cognitive impairment, gastrointestinal problems, and psychosis have been "mostly ignored by the field, because it has been so focused on predominant motor symptoms," he said.

Indeed, there are few therapies specifically approved to treat the non-motor symptoms of PD, and a large portion of the pharmacological treatments used for non-motor symptoms are given off label. These include quetiapine and clozapine for PD psychosis, amitriptyline for PD depression without dementia, and modafinil for patients with excessive daytime sleepiness.

Acadia Pharmaceuticals' Nuplazid (pimavanserin) has proven to be a groundbreaking approach to addressing the non-motor symptoms of PD, specifically hallucinations and delusions. Datamonitor Healthcare forecast sales of Nuplazid to reach peak sales of $582m in 2026. However, there still exists a wide range of non-motor complications that significantly impact patients' quality of life that are not adequately addressed. Promisingly, Anavex Life Sciences' ANAVEX 2-73 has shown potential in improving cognitive function in dementia patients during Phase II trials. According to Phase IIb data, Enterin Inc's ENT-01, appears to also have high efficacy in addressing multiple non-motor symptoms such PD-related constipation, psychosis, and dementia.

Alpha-Synuclein

"At UCB, we try to really understand the path of biology of the disease, and in Parkinson's it's clear that alpha-synuclein plays a critical role," said Citron, adding that unlike amyloid beta in Alzheimer's disease, "it is not only causally involved in Parkinson's patients, but it also drives the progression of the disease."

Alpha-synuclein is a protein that is primarily found in the brain, particularly in the presynaptic terminals of neurons. In PD, alpha-synuclein undergoes abnormal changes in its structure and forms aggregates called Lewy bodies. These Lewy bodies are one of the hallmarks of Parkinson's disease and are found in brain cells, specifically in the substantia nigra region.

While the discovery that alpha-synuclein plays a critical role in the pathogenesis of PD is now twenty-five years old, it still represents a milestone in PD research as the industry works to target this protein. UCB is studying UCB0599 in a development and commercialization partnership with Novartis, in Phase II. The asset is a potential first in class, small molecule, alpha-synuclein misfolding inhibitor. This asset, alongside an anti-alpha-synuclein antibody Phase I candidate, UCB7853, form part of a deal with the Swiss major that could net UCB $1.5bn if clinical and regulatory milestones are hit. (Also see "*Novartis Will Co-Develop UCB's Alpha-Syn Inhibitor For Parkinson's*" - Scrip, 2 Dec, 2021.)

> *"We try to really understand the path of biology of the disease, and in Parkinson's it's clear that alpha-synuclein plays a critical role." - Martin Citron, UCB*

UCB is of course not the only drug company targeting alpha-synuclein, the list of runners and riders is extensive. Anovis, ABL Bio, Kainos Medicine Inc., BioArctic, AstraZeneca, AC Immune, PTC Therapeutics, and Vaxxinity all have pipeline drugs targeting the protein.

In fact, it may be the targeting of the alpha-synuclein protein that provides the first disease modifying therapy in the PD market. Prothena's monoclonal antibody prasinezumab, developed in partnership with Roche, demonstrated promising proof of concept in initial trials, and achieved a significant average reduction of 96% in free serum alpha-synuclein levels among healthy volunteers.

Breaking Through The Diagnostics Odyssey

The journey to PD diagnosis can be a long and winding road, especially when early symptoms can be heterogenous across different individuals. Patients present with symptoms that could be related to many other conditions. Diagnosis still relies on subjective clinical interpretation by a neurologist or specialist. “We certainly need better, more objective diagnostic tools,” said Frasier.

MJFF has been funding biomarker research since the 2000s, and innovation is starting to materialize. Until recently there was no universal biomarker for the condition, however in April the Foundation was able to announce that it had funded a “an enormous leap forward” by finding a biomarker for the disease. The tool, called the alpha-synuclein seeding amplification assay (αSyn-SAA), can detect pathology in cerebrospinal fluid (CSF) not only of people diagnosed with Parkinson’s, but also in individuals who have not yet been diagnosed or shown clinical symptoms of the disease, but are at a high risk of developing it.

The assay can confirm the presence of abnormal alpha-synuclein, detected in most people with PD, with astonishing accuracy: 93% of people with Parkinson’s who participated in the assay were proven to have abnormal alpha-synuclein. Until recently a drop in dopamine levels was the only biological test that could allude to a general marker of Parkinsonism, but not specifically to Parkinson's disease.

This biomarker is an important tool for clinical trials. Researchers are able to ensure enrolled volunteers have the specific altered biology which enriches the population. The biomarker was found through the Parkinson’s Progression Markers Initiative (PPMI), a study launched in 2010 with a mission to identify biomarkers of PD onset and progression.

“With this breakthrough, my general opinion is that innovation is going to happen very rapidly, because now it’s been shown in the PPMI study,” said Frasier. “It can be done in spinal fluid, there are several different approaches to do it in other tissues like blood or nasal swabs or skin.

So I think this will be an area where we'll see a lot of innovation and rapid development and improvement. I'm optimistic. Data in the last six months has really made me excited about the future of these biomarkers and diagnostics," he told *In Vivo*.

University of Manchester researchers analyzing sebum with mass spectrometry found that there are lipids of high molecular weight that are substantially more active in people suffering from PD. And a recent paper published in *Nature Medicine* showed Japan's Juntendo University's highly sensitive blood test that can accurately identify people with synucleinopathies. Microscopic analysis detected structural differences between aggregates derived from seeds isolated from patients with different synucleinopathies such as PD, *Lewy Body dementia* and *multiple system atrophy*.

This approach makes the test for PD scalable, commented UCB's Citron. "Many people are hesitant to get a CSF tap, and it's something that not every general practitioner is going to be comfortable doing. But everybody can draw blood, you can scale. It's cheaper for the healthcare system as well. This is probably one of the most exciting areas of research right now," he said.

A diagnostic that also promises to seek out early signs of PD, but with less risk than extracting spinal fluid, is the NeuroMotor Pen, developed by Manus Neurodynamica. It finds digital biomarkers by applying artificial intelligence to the data produced by the device. The technology is deceivingly simple, the pen has built-in highly accurate sensor technologies, combined with analytical software, that processes minute limb and hand motion parameters to quantify fine motor skills, making brain scans redundant. (Also see "*Manus Neurodynamica: Catching Up With A 2022 Rising Leader*" - In Vivo, 21 Jun, 2023.)

"This test can be done anywhere where it's needed, you can go into a patient's home or in the pharmacy, anyone can be trained in 15 minutes to administer the test," explained Rutger Zietsma, founder of Manus Dynamica and inventor of the technology.

Regular use of the NeuroMotor Pen also enables the clinician to monitor the patient's response to medication and disease progression, Zietsma said.

AI is having a huge impact on the detection of neurodegenerative conditions, but it is also a new weapon in the armamentarium of assistive technologies, telemedicine and disease management.

"The challenge there [with digital sensors] is linking that to the patient experience. From a regulatory perspective, the regulators need to know if a smartwatch pattern is detecting Parkinsonian movements, and how that relates to how someone feels or functions. The regulators are looking to bridge that objective sensor to actual living experience," explained Frasier.

A Cure Within A Generation?

Equal to the amount of innovation in therapeutics and diagnostics is the amount of hope felt by those closely involved in the field of research into Parkinson's disease. There are still significant hurdles to overcome such as the commercialization of new therapies in non-motor symptoms, and full clinical evidence of a disease modifying drug. However, breakthroughs in detecting pathology before symptoms appear could push PD finally into a curative space, something that Citron believes is not "completely off the table at this point."

While it is difficult to predict the exact timeline, it is certainly possible that significant strides will be made in PD research within a generation. Even if a complete cure is not achieved, continued advancements will lead to improved treatments, better management strategies, and enhanced quality of life for individuals living with Parkinson's disease.