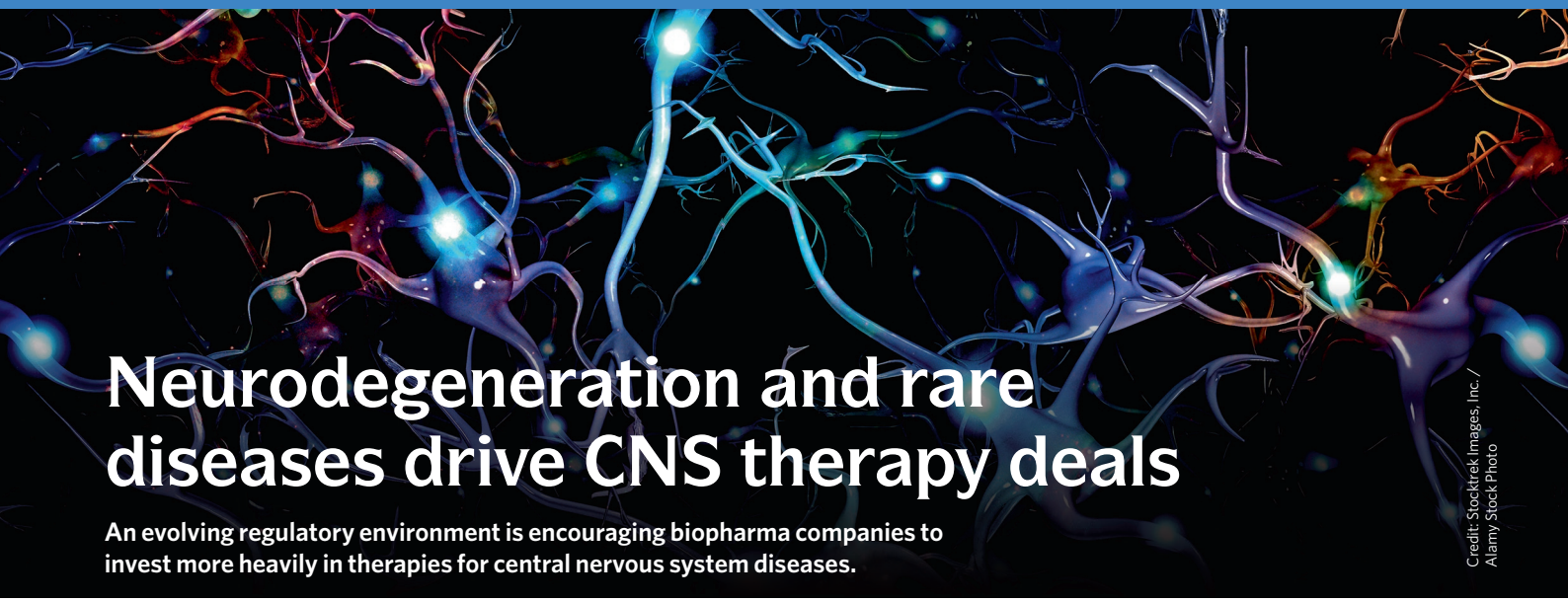

Neurodegeneration and rare diseases drive CNS therapy deals

An evolving regulatory environment is encouraging biopharma companies to invest more heavily in therapies for central nervous system diseases.

Mark Zipkin

For decades, the dream of disease-modifying therapies for neurodegenerative disorders has spurred development in the central nervous system (CNS) disease field from companies, supported by major investments reflecting the high hopes. However, such investments have regularly culminated in clinical trial failures and companies exiting the area. In the wake of the recent approvals of Biogen's Aduhelm (aducanumab) and Biogen/Eisai's Leqembi (lecanemab) for Alzheimer's disease by the United States Food and Drug Administration (FDA), dealmaking in the CNS area this year is on track to top 2022, but it remains unclear whether better understanding of disease biology and a regulatory environment in which surrogate endpoints have become increasingly accepted have finally put the field on more stable ground.

When Aduhelm was granted an FDA accelerated approval in 2021, it was a watershed moment. "Aduhelm definitely marked an important transition point in the space," said Laura Chico, senior vice president of equity research at investment firm/wealth management company Wedbush Securities, based in Chicago, Illinois, US. However, she added, "We haven't necessarily seen that translate to more CNS-focused mergers and acquisitions (M&A) at this point. In general, there's perhaps been a little bit of concern on the investor side as to the implications of the Inflation Reduction Act (IRA)." The IRA is a US federal law, signed in 2022, which enables the Department of Health and Human Services to negotiate certain drug prices through Medicare—a government healthcare national insurance program for people aged over 65 and some younger people with certain condition. Despite industry objections, this is expected to lead to reduced prices for some prescription drugs.

If CNS drug research was about to hit its stride, the timing was not ideal. The industry downturn following the massive increase in spending during the pandemic has pushed biotech companies into a period of consolidation. Chico said US-based exchanges have lost one-quarter of public biotechs with over $500 million market cap since January 2022—most likely with further contraction yet to come. "But in prior periods of consolidation, it's happened faster and it's happened deeper," she added.

Neurodegeneration regeneration

Despite these difficult conditions, neurodegenerative disease deal flow has increased over last year, with more than $15 billion pledged in deals with disclosed values. All told, four of the seven deals so far this year worth a potential $1 billion or more are focused on neurodegeneration (Table 1).

Alzheimer's disease was the busiest CNS indication for biopharma companies in 2023 (Table 1). In 2022, there were at least 44 deals—including partnerships and M&A—for Alzheimer's-focused companies. So far this year (through to October 24, 2023), companies have disclosed another 37 deals potentially worth more than $4 billion. The biggest among them is Bristol Myers Squibb's (BMS's) acquisition of anti-tau antibody PRX005 from Prothena, based in San Francisco, California, US, exercising an earlier option for worldwide rights that could be worth $2.2 billion with milestone payments.

Misfolded tau proteins cause neurofibrillary tangles that are a hallmark of Alzheimer's disease, and BMS isn't alone in targeting tau. In April, Takeda teamed up with Canadian biotech Treventis Partners, based in Toronto, Canada, to develop anti-tau small molecules in a deal worth up to $372.5 million in milestones. Tau represents a distinct therapeutic opportunity from the hallmark amyloid-beta plaques that are targeted by Aduhelm and Leqembi, although the two pathways interact.

Several pharma companies are investigating synergies between the different mechanisms. "Amyloid-beta is a long-known hypothesis, but now it's been demonstrated to deliver a cognitive benefit. We're particularly interested in other mechanisms like tau-lowering, for example, which we think is a really important driver with Alzheimer's disease," said Adam Keeney, head of corporate development at Biogen. "We're thinking about the combinations of amyloid-beta and tau to really get to a significant improvement in cognitive decline." Keeney noted that Biogen has a tau-lowering antisense oligonucleotide (ASO) therapy that is currently in phase 1 trials.

The Parkinson's disease space is on a similar trajectory, with companies exploring a variety of possible therapeutic pathways. In January 2023, Neurocrine Biosciences, based in San Diego, California, partnered with Voyager Therapeutics, based in Cambridge, Massachusetts, on a multi-target gene therapy development deal that could be worth up to $4.4 billion. To start, Neurocrine paid $175 million upfront in cash and equity to pursue a Parkinson's treatment strategy targeting *GBA1* gene replacement.

In March 2023, Biohaven, based in Newhaven, Connecticut, US, obtained global rights (outside of China) from Hangzhou Highlightll Pharmaceutical Co. to BHV-8000, a dual tyrosine kinase 2 (TYK2) and janus kinase 1 (JAK1) inhibitor. The companies believe these immune targets could impact neurodegenerative diseases and neuroinflammatory disorders including Parkinson's, amyotrophic lateral sclerosis (ALS), and Alzheimer's. Biohaven paid an initial $20 million in cash and equity, with another $950 million in development and commercial milestones.

In October, Chicago-based AbbVie picked up San Francisco-based Mitokinin, which is targeting PINK1 enzyme activation in a separate pathway to improve mitochondrial dysfunction, a possible driver of Parkinson's disease pathogenesis and progression. At closing, Mitokinin will receive $110 million, with the potential for

Table 1 | Selected partnering deals in the CNS field in 2023

Date	Companies 1 and 2	Deal value ($ million)	Deal summary
January 2023	Genentech; Belharra Therapeutics	2,080	Genentech plans to develop small molecules discovered by Belharra Therapeutics for neurodegenerative diseases and other therapeutic areas. Belharra received $80 million cash upfront, with potential for more than $2 billion more in milestone and royalty payments, to move assets discovered with its chemoproteomics platform through early preclinical development. Genentech will progress candidates from late preclinical through commercialization.
April 2023	Johnson & Johnson Innovative Medicine; Pipeline Therapeutics	1,080	Pipeline Therapeutics will co-develop PIPE-307, its clinical-stage M1 muscarinic receptor antagonist for nervous system disorders, with Janssen Pharmaceuticals. Janssen and its parent company, Johnson & Johnson Innovative Medicine, pledged $75 million upfront in cash and equity, with potential for $1 billion more in milestone and royalty payments. Pipeline is preparing to launch a phase 2 study in patients with relapsing-remitting multiple sclerosis.
January 2023	Neurocrine Biosciences; Voyager Therapeutics	4,400	Neurocrine Biosciences is partnering with Voyager Therapeutics to advance its lead preclinical gene therapy delivering *GBA1* for Parkinson's disease, as well three other rare central nervous system disease preclinical programs. Neurocrine paid $175 million in cash and equity, and Voyager is eligible for an additional $1.5 billion in milestones and $2.7 billion in profit-sharing. The deal builds on a similar pact for Parkinson's and Friedriech's ataxia candidates in 2019.
July 2023	Bristol-Myers Squibb; Prothena Corporation	2,200	Bristol Myers Squibb executed an option for commercial rights to Prothena Corporation's PRX005, an anti-tau antibody currently in phase 1 testing for Alzheimer's disease. Prothena received $55 million and is eligible for $270 million more for United States and global commercial rights, plus another $1.7 billion in milestone payments.
July 2023	Novartis; DTx Pharma	1,000	Novartis purchased siRNA company DTx Pharma for $500 million, with the potential of another $500 million in milestone payments. DTx developed siRNA therapies for central and peripheral nervous system diseases, as well as the neuromuscular rare disease, Charcot-Marie-Tooth disease.
July 2023	Biogen; Reata Pharmaceuticals	7,300	Biogen acquired neurological disease company Reata Pharmaceuticals for $7.3 billion. Reata just launched Skyclarys (omaveloxolone), approved by the United States Food and Drug Administration earlier this year and under regulatory review in Europe to treat Friedreich's ataxia.
September 2023	Genentech; Orionis Biosciences	2,050	Genentech is collaborating with Orionis Biosciences on molecular glues for neurodegenerative and oncology indications. Orionis will be responsible for discovering small molecules against targets chosen by Genentech, while Genentech will handle development from late preclinical stages through commercialization. Genentech paid $47 million upfront, with the potential for more than $2 billion in milestone payments and royalties.

another $545 million in development and commercial milestone payments, as well as royalties.

Medium-rare

In the past, many companies had moved away from CNS therapy development because of gaps in the biology and regulatory uncertainty regarding how to approach clinical trials, said Keeney. "I think over the last ten years that that has really changed. Now you actually see a resurgence of interest in neuro and a new level of investment from pharma but also from biotech and VCs [venture capitalists]."

He attributes the change to the openness of regulatory authorities to scientific-driven hypotheses, not only around the processes of driving disease but also what endpoints and biomarkers can expedite development in areas that have historically been very challenging. As with amyloid beta, Biogen has engaged with the FDA to establish lower levels of neurofilament light (NfL) as an endpoint for accelerated approval in ALS. In June, Biogen disclosed a partnership with Israeli biotech NeuroSense Therapeutics, based in Herzilya, to evaluate whether a clinical asset lowers NfL levels in patients with ALS.

Rare CNS disease deals may have already topped 2022 with at least 47 deals announced this year (Fig. 1).

Among rare CNS diseases, interest in ALS has remained high this year. Takeda and AcuraStem, based in Monrovia, California, announced a licensing agreement to develop ASO therapies for the treatment of ALS and other proteinopathies like frontotemporal dementia, with upfront and milestone payments worth up to $580 million.

Overall, at least 49 deals have been announced so far in 2023 involving rare diseases, with disclosed values totaling $13.2 billion — more than twice the totals from all of 2022. A major driver was Biogen's acquisition of Reata Pharmaceuticals, based in Plano, Texas, US, for $7.3 billion. Reata's Skyclarys (omaveloxolone) in February became the first approved therapy for the rare neurodegenerative disease, Friedreich's ataxia. Keeney said the deal was a natural fit for Biogen's evolving rare disease strategy, given an existing portfolio that includes the gene therapy Spinraza (nusinersen) for another rare neurodegenerative disease, spinal muscular atrophy.

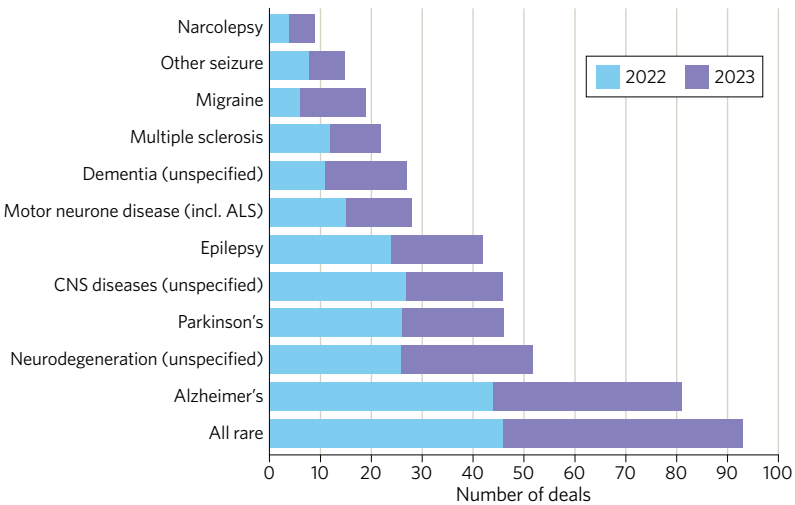

Fig. 1 | Neurological disease deals by therapy type in 2022 and 2023 (October). Source: Cortellis 2023. Neurological disease deals from 01 January 2022 to 24 October 2023. ALS, amyotrophic lateral sclerosis.

The deal is encouraging and stands out to Chico, "partly because I think it signifies the importance of orphan disease therapies." With the backdrop of the IRA, many have been concerned about a shift away from a focus on orphan indications. "I do think orphan therapies are still at a premium, which is positive for the sector."

Multiple companies are pursuing nucleic acid therapies for rare CNS indications, including at least three pacts in gene therapy, three in gene silencing, and one in mRNA. The largest was Novartis's purchase of siRNA company DTx Pharma. While the lead preclinical asset is in rare peripheral nerve disease Charcot-Marie-Tooth disease type 1A, Novartis also acquired CNS and neuromuscular preclinical programs. Novartis paid $500 million upfront with potential for another $500 million in milestone payments.

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