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Biogen pays $560m for an unproven Parkinson's mechanism

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All the attention is on aducanumab, but yesterday's deal with Denali is a reminder that Biogen has other irons in the fire.

With its Alzheimer's project aducanumab, Biogen is nearing a knife-edge decision that will change its fortunes markedly. Away from this life-or-death event, however, the more normal business of operating a biotech company goes on.

And in paying $560m upfront to Denali Therapeutics yesterday in exchange for rights to its phase I-stage Parkinson's disease therapy and a handful of other projects, Biogen has forged one of the biggest licensing deals of the year.

The partners will co-develop and co-promote the various projects, with rights varying in different territories. As well as the upfront fee, the agreement will see Biogen take an 11% stake in Denali with a $400m equity investment; at around $35 per share this comes in at a 50% premium to Denali's closing price on Wednesday. At the back end, Denali is in line for another $1.1bn in milestones as well as royalties.

Chief among the molecules Biogen has licensed is DNL151, which will enter late-stage testing next year. One trial will enrol Parkinson's patients with a kinase-activating mutation in the leucine-rich repeat kinase 2 (LRRK2) gene and the other patients with sporadic disease. LRRK2 is a regulator of lysosomal function, and mutations in the gene can cause Parkinson's as well as lysosomal dysfunction, which contributes to neurodegeneration. Denali says that its LRRK2 inhibitors could slow the progression of Parkinson's – there is no suggestion that it could halt or reverse the disease.

Biogen is not a stranger to LRRK2-targeting drugs. It is collaborating with Ionis Pharmaceuticals on development of BIIB094, an antisense oligonucleotide targeting the gene. A phase I multiple ascending intrathecal dosing trial, Reason, began last year in 82 Parkinson's subjects with or without verified LRRK2 mutations. Data are expected in 2022.

Biomarker data

DNL151 is more advanced than this – but not by much, having only generated limited biomarker data in phase Ib. In January Denali said the Roche-originated project achieved "target and pathway engagement" of greater than 50% and a dose-dependent reduction of the lysosomal biomarker BMP in urine of up to 50%. It was generally safe and well tolerated at all doses tested, prompting Denali to expand DNL151's phase 1 and 1b

clinical trials to study higher doses.

All in all, DNL151 has been dosed in 162 healthy volunteers in a phase I trial and 25 Parkinson's patients in a phase 1b study. These are ongoing, though in April the group said dosing had been paused owing to the Covid-19 pandemic. The other LRRK2 inhibitor it had been developing in Parkinson's, DNL201, has been shelved, since '151 had better pharmacokinetics (*Crunch time for the new Parkinson's hopes, February 18, 2020*).

LRRK2 is a complicated protein-kinase complex with many purported functions, and despite Denali's statements its role in Parkinson's is not entirely clear. DNL151 inhibits wild-type LRRK2 as well as the mutated forms, and there is a chance that this might have unintended consequences. Proof of whether '151 can actually improve symptoms, or will be safe over the long term, will not emerge for a couple of years, and the same is true of the other earlier stage programmes.

But Biogen has apparently seen something in '151 and the other LRRK2 inhibitors covered by the deal – one of which appears to be the preclinical Crohn's disease project DNL975 – that is worth more than $1bn. But the agreement covers other candidates too, and perhaps part of the lure was Denali's transport vehicle (TV) technology.

As well as '151 and the other LRRK2 inhibitors, Biogen's license entitles it to exclusive options to two other programmes for neurodegenerative diseases that use the TV platform, which enables proteins to cross the blood-brain barrier – including one for amyloid beta. Separately it has right of first negotiation for two unnamed preclinical projects that use the TV platform.

The TV technology is popular; in 2018 Takeda took options to three of Denali's TV-based preclinical programmes, including two in Alzheimer's disease, for $40m up front and $110m in equity (*Takeda forges another neuroscience deal as Abbvie dips a toe, February 20, 2018*).

Even including the potential of the TV technology, this deal involves paying huge amounts for some early Parkinson's therapies, only one of which has even reached phase I. It's a heck of a bet. But this is the company that has brought aducanumab all the way to the FDA's door – Biogen clearly has nerves of steel.

2020 big bucks: largest up fronts paid for clinical-stage projects

Project (status at deal)	Company	Deal partner	Upfront value ($m)
DS-1062 (phase I)	Astrazeneca	Daiichi Sankyo	1,000
Tafasitamab (filed)	Incyte	Morphosys	750
Epcoritamab (phase I/II), GEN3009 (phase I), GEN1044 (IND filed)	Abbvie	Genmab	750
Pralsetinib (phase III)	Roche	Blueprint Medicines	650
LRRK2 inhibitor program including DNL151 (phase I)	Biogen	Denali	560

Note: Excludes any equity investments made as part of deal. Source: EvaluatePharma.