Crunch time for the new Parkinson’s hopes

Elizabeth Cairns

Clinical results this year from companies including Roche, Biogen and Sanofi should show whether new drug classes can arrest the development of Parkinson’s disease.

Decades of drug development for Parkinson’s disease have yielded little beyond levodopa, used to control the movement disorders symptomatic of the condition. No therapy capable of halting or reversing patients’ neurodegeneration has come to light.

Several mid-stage trials set to read out this year ought to show which, if any, new mechanisms might stand a chance of halting the progression of Parkinson’s. Chief among these mechanisms is the alpha-synuclein hypothesis, and imminent phase II data on rival inhibitors of this protein, being developed by Roche and Biogen, ought to show whether the theory has legs.

The basis for the hypothesis is that several mutations in the alpha-synuclein protein cause autosomal dominant forms of Parkinson’s, while others, which increase alpha-syn expression, are linked to a higher-than-normal risk of the disorder. Spherical, aggregated forms of the protein – Lewy bodies – are a hallmark of Parkinsonian neuropathology.

The wages of syn

First up are data from the two-part Pasadena trial of Prothena’s anti-alpha-syn MAb PRX002, licensed to Roche in 2013. Pasadena’s first part tests a high dose (4,500mg for patients with bodyweight of 65kg or more, and 3,500mg for those who weigh less), a low dose (1,500mg) and placebo. At the end of part one, after a year, patients from the placebo group will be randomised to either high or low-dose PRX002 for another year.

The primary endpoint is change from baseline in patients’ score on the Movement Disorder Society-unified Parkinson’s disease rating scale (MDS-UPDRS) after one year – that is, after part one. Data will come this year, Prothena said last week.

The phase II Spark trial of Biogen’s BIIB054 is perhaps less useful as proof of the alpha-syn concept. Spark is of a similar size and design to Pasadena, testing three doses of the MAb versus placebo, with an interim readout at one year. But its endpoints do not look at patient outcomes.

Instead the primary measure is the rate of adverse events, while secondaries are geared towards the pharmacodynamic effects of BIIB054 on dopaminergic nerves, as well as its pharmacokinetics and
immunogenicity. Data on safety and possibly also pharmacodynamics are expected in the second half of 2020.

A tiny phase I/II trial and an even tinier extension study of the cerebral dopamine neurotrophic factor formulation under development by Herantis Pharma ought to yield data this year too. According to the Finnish group CDNF not only protects neurons from degeneration, it also restores the function of already degenerating neurons. It functions in several ways, the company contends, one of which is inhibiting the formation of alpha-synuclein oligomers, so this could play into the alpha-syn theory too.

Despite the small size of these trials they are assessing a whole suite of endpoints – the initial trial has 11 primary endpoints and the extension 25, according to clinicaltrials.gov. The value of the conclusions that can be wrought from these small trials is open to question; data are expected in the first quarter.

Swimming upstream

Data on Anavex’s ANAVEX2-73, also called blarcamesine, are expected mid-year. The project is a sigma-1 receptor ligand that Anavex says acts upstream from other targets, activating neuroprotective signals that help neurons return to homeostasis. The company has exploratory phase II data suggesting that the project can improve cognition in Alzheimer’s patients, but there are so far no human data in Parkinson’s.

The phase II Parkinson’s trial will assess the effect of two doses on a computer-based cognition test, as well as the molecule’s safety, versus placebo.

The other big-cap pharma trying a new attack is Sanofi. GZ402671, aka venglustat, is in development for several rare disorders associated with mutations in the glycosphingolipid metabolic pathway. The Moves-PD trial has enrolled Parkinson’s disease patients with a mutation in the GBA gene.

This mutation is one of the most common genetic risk factors for Parkinson’s; 5-10% of patients carry the variant, making it a more common mutation than that in the alpha-synuclein gene. Patients with the GBA mutation tend to experience motor symptom deficits and cognitive decline more rapidly than others.

Moves-PD has a pretty solid endpoint: change from baseline in MDS-UPDRS Part II and III score at two months, and again at one year. In the almost unimaginably unlikely event that both Moves-PD and Roche and Prothena’s Pasadena trial hit, Sanofi’s project could reach a wider population.

The following analyses exclude investigator-initiated trials and those that are due to report after 2020. They also exclude gene therapies for Parkinson’s, which are covered separately here.

<table>
<thead>
<tr>
<th>Company</th>
<th>Project</th>
<th>Pharmacological class</th>
<th>Trial ID</th>
<th>N</th>
<th>Primary completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roche/Prothena</td>
<td>PRX002/RO7046015 (prasinezumab)</td>
<td>Anti-alpha-synuclein MAb</td>
<td>Pasadena (NCT03100149)</td>
<td>316</td>
<td>Dec 2019</td>
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<tr>
<td>Biogen</td>
<td>BIIB054 (cinpanemab)</td>
<td>Anti-alpha-synuclein MAb</td>
<td>Spark (NCT03318523)*</td>
<td>311</td>
<td>May 2020</td>
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<td>Herantis Pharma</td>
<td>CDNF Parkinson’s Project</td>
<td>Cerebral dopamine neurotrophic factor</td>
<td>NCT03295786 &amp; NCT03775538</td>
<td>17 and 15</td>
<td>Dec 2019 &amp; Jun 2020</td>
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<td>Anavex Life Sciences</td>
<td>ANAVEX 2-73 (blarcamesine)</td>
<td>Muscarinic &amp; sigma-1 receptor agonist</td>
<td>NCT03774459</td>
<td>120</td>
<td>Jul 2020</td>
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<td>Sanofi</td>
<td>GZ402671/SAR02671 (venglustat malate)</td>
<td>GCS inhibitor</td>
<td>Moves-PD (NCT02906020)</td>
<td>270</td>
<td>Dec 2020</td>
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</table>

Source: EvaluatePharma & Stifel. *Also in a phase I trial in Japan (NCT03716570).

Several novel mechanisms are also being evaluated in phase I studies, though naturally these will yield few definitive conclusions on the disease-modifying nature of the therapies.

Two more anti-alpha-synuclein MABs are in phase I: Takeda and Astrazeneca’s TAK-341 and Lundbeck’s Lu AF82422. Neither is expected to post data on clinical benefit.

Denali Therapeutics has two shots on goal here, with the leucine-rich repeat kinase 2 inhibitors DNL201 and DNL151. LRRK2 is a regulator of lysosomal function, which is impaired in Parkinson’s disease, contributing to the formation of Lewy bodies and neurodegeneration.

These trials read out a month ago, with DNL201 meeting all biomarker goals and being generally well tolerated.
at the lower dose tested. DNL151 was well tolerated at both the doses in the trial, and met all safety and biomarker goals. DNL151’s phase 1b trial has been expanded to study higher doses.

In the coming months Denali intends to choose either DNL201 or DNL151 to take into phase II/III trials in Parkinson’s.

FB-101, targets c-Abl, which the South Korean group 1ST Biotherapeutics claims plays a role in driving alpha-synuclein pathogenesis in Parkinson’s. The compound is thought to be the first c-Abl inhibitor to advance into clinical trials, and its single and multiple ascending-dose study should report this year.

### Selected phase I potentially disease-modifying projects for Parkinson's disease

<table>
<thead>
<tr>
<th>Company</th>
<th>Project</th>
<th>Pharmacology</th>
<th>Trial ID</th>
<th>N</th>
<th>Primary completion</th>
</tr>
</thead>
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<td>Denali/Roche</td>
<td>DNL201</td>
<td>LRRK 2 inhibitor</td>
<td>NCT03710707</td>
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<td>Trial hit</td>
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<tr>
<td>Denali/Roche</td>
<td>DNL151</td>
<td>LRRK 2 inhibitor</td>
<td>NCT04056689</td>
<td>34</td>
<td>Trial hit</td>
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<td>Lundbeck/Genmab</td>
<td>Lu AF82422</td>
<td>Anti-alpha-synuclein MAb</td>
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<td>Jan 2020</td>
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<td>1ST Biotherapeutics</td>
<td>FB-101/IST-102</td>
<td>c-Abl kinase inhibition</td>
<td>NCT04165837</td>
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<td>Mar 2020</td>
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<tr>
<td>Takeda/Astrazeneca</td>
<td>TAK-341/MEDI1341</td>
<td>Anti-alpha-synuclein MAb</td>
<td>NCT03272165</td>
<td>48</td>
<td>Nov 2020</td>
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*Source: EvaluatePharma & Stifel.*

Of these trials, Pasadena and Moves-PD are the ones to watch since they should reveal the effects their differing mechanisms have on the development of Parkinson’s. As with Alzheimer’s and plenty of other CNS disorders, the extent of the difficulty of showing a definite effect on disease progression is matched only by the vastness of the rewards to be gained from success.

This difficulty is reflected in the consensus forecasts compiled by *EvaluatePharma*. The only one of the above projects to have sales numbers attached is PRX002: in 2024 it is forecast to sell just $3m.

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