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Therapy focus – Novel Parkinson's projects gather pace

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Last week's acquisition of Prexton by Lundbeck – along with recent data on Voyager's gene therapy – raised hopes of a new era in Parkinson's disease. Levodopa has been the mainstay of therapy for decades, but does not slow the progression of the disease and is associated with troublesome side effects.

While the projects in late-stage development mainly comprise different formulations of levodopa, the mid-stage pipeline is surprisingly crowded, with several new mechanisms in play (see table below). The compound that Lundbeck picked up with Prexton, foliglurax, is a case in point.

First in class

Foliglurax is a first-in-class mGluR4 regulator, and initial phase II data are expected in the first half of 2019, when it should become apparent whether Lundbeck made a good bet – the Danish company paid €100m ($123m) up front and is on the hook for up to €805m in milestones.

While current treatments aim to replace the dopamine lost in Parkinson's or mimic its effects, foliglurax takes a different approach by increasing mGluR4 activity. This is thought to reduce activity in the brain pathway that inhibits movement, which is dominant in Parkinson's disease, thereby restoring movement.

Because mGluR4 receptors are found in a part of the brain that is largely unaffected by Parkinson's disease, it is hoped that foliglurax might escape one of the major problems seen with levodopa, namely that the drug becomes less effective over time as the brain degenerates.

Still, foliglurax does not promise a cure, and neither does Voyager's gene therapy VY-AADC01. The latter is essentially designed to bolster levodopa's efficacy by targeting the gene for the enzyme that converts levodopa to dopamine. Voyager reported promising but early data this month (*Voyager still has a long way to go with Parkinson's gene therapy, March 9, 2018*).

VY-AADC01 could soon leapfrog the projects in the list below, since Voyager plans to start a phase II/III trial in the middle of this year. Results should be available in 2020, the company has told *EP Vantage*.

Selected novel Parkinson's disease projects in phase II development				
Project	**Company**	**Description**	**Trial(s)**	**Primary completion**
KM819	Kainos Medicine	FAS associated factor 1 inhibitor	NCT03022799	Jul 2017
SAGE-217	Sage Therapeutics	GABA A receptor regulator	NCT03000569	Sep 2017
Eltoprazine	Amarantus Bioscience	5-HT2C receptor antagonist; 5-HT1A receptor partial agonist; 5-HT1B receptor partial agonist	NCT02439125	Jun 2017
EPI-589	Sumitomo Dainippon Pharma	Redox cofactor	NCT02462603	Apr 2018
ITI-214	Intra-Cellular Therapies	PDE1 inhibitor	NCT03257046	May 2018
Ferriprox	Apotex	Iron chelator	Fairparkii, NCT02655315	Dec 2018
Foliglurax	Prexton (now Lundbeck)	mGluR4 regulator	Ambled, NCT03162874; Attuned, NCT03331848	Dec 2018; Feb 2019
CX-8998	Cavion	Calcium channel Cav3.2 blocker	NCT03436953	Jun 2019
Liraglutide (Victoza/Saxenda)	Novo Nordisk	GLP-1 receptor agonist	NCT02953665*	Jul 2019
CDNF Parkinson's Project	Herantis Pharma	Cerebral dopamine neurotrophic factor	NCT03295786	Aug 2019
PRX002	Prothena	Alpha-synuclein accumulation antibody	Pasadena, NCT03100149	Mar 2020
GZ402671	Sanofi	Glucosylceramide synthase inhibitor	Moves-PD, NCT02906020	Mar 2021
BIIB054	Biogen	Alpha-synuclein accumulation antibody	Spark, NCT03318523	Apr 2021
GM608	Genervon Biopharmaceuticals	GM6 analogue	-	-

**Investigator-sponsored trial; Source: EvaluatePharma, Clinicaltrials.gov.*

As for other candidates that might soon go into late-stage trials, Sage Therapeutics has said that it will continue development of SAGE-217 in Parkinson's. However, the company's main focus for the project is depression.

South Korea's Kainos Medicine aims to slow down the cell death seen in Parkinson's with its novel FAF1 inhibitor KM819, but results from a phase II study that had been due to conclude last year have not yet materialised.

It is also unclear what has delayed Genervon's GM608 – a phase IIa trial of that project in Parkinson's finished in 2014, according to Clinicaltrials.gov; the company said in February that it was planning further phase II development in this indication.

Multiple mechanisms

The list above reveals that companies are trying many different ways of tackling Parkinson's. An interesting approach comes from an investigator-sponsored study of Novo Nordisk's diabetes/obesity drug liraglutide in the neurodegenerative disease.

It is thought that GLP-1 agonists like liraglutide could protect nerve cells from the damage seen in Parkinson's as well as Alzheimer's. Novo's chief science officer, Mads Krogsgaard Thomsen, has previously told *EP Vantage* that the company's next generation GLP-1, semaglutide, might be even more effective here because

of its ability to cross the blood-brain barrier (*Interview – Semaglutide holds the key to Novo's success, October 3, 2017*).

Another potentially disease-modifying approach could come from targeting alpha-synuclein. Because this protein clumps together to form Lewy bodies, which are hallmarks of Parkinson's, it is hoped that this could slow disease progression.

Two companies have alpha-synuclein accumulation antibodies in phase II, according to *EvaluatePharma*: Biogen and Prothena. The latter recently got a boost from a deal with Celgene, though the Parkinson's project looks unlikely to be covered by that agreement, which focused on tau, TDP-43 and a third, undisclosed target.

Other gene therapy approaches also hold promise. Oxford Biomedica has shifted away from the failed OXB-101/Prosavin, and plans to take a next-generation candidate, OXB-102, which it says has a more potent vector construct, into a phase I/II trial soon.

But this would not be a disease-modifying therapy; OXB-102 is designed to alter cells in the brain's striatum to produce dopamine, so it would work in a similar way to levodopa. Still, the company believes that a single administration could produce an effect for years and not be affected by the gradual loss of efficacy seen with levodopa.

All of these projects are some way from the market. The next Parkinson's therapy up for approval is Acorda Therapeutics' inhaled levodopa Inbrija, which would not represent a huge shift away from current practice. Further behind are several candidates that, if successful, could help rejuvenate the stale Parkinson's space.

This study has been updated to reflect the fact that the trial of liraglutide is investigator sponsored.

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