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Therapeutic focus – Treating dyskinesia proves as elusive as Parkinson's itself

Jacob Plieth

At a time when repeated failures in developing a drug for Parkinson's disease to reduce or eliminate levodopa are keeping alive the rationale for targeting the mainstay treatment's side effects, this too has suffered its share of knockbacks.

Just this week Novartis quietly discontinued mavoglurant for levodopa-induced dyskinesia, arguably clouding the future for Addex Pharmaceuticals' dipraglurant, which uses the same mechanism of action. One of the few positive recent developments in this shrinking space is the start of enrolment into a phase II trial of Avanir's AVP-923 (see table below).

Mavoglurant had been one of the most advanced industry projects for treating levodopa-induced dyskinesia (LID) – the uncontrollable, jerky movements that characterise long-term use of levodopa. Buried deep within Novartis's third-quarter report was news of its discontinuation in LID on lack of efficacy in a 154-patient phase II study; the project remains alive in Fragile X syndrome.

The agent is a negative allosteric modulator of metabotropic glutamate receptor 5 (mGluR5), a mechanism at whose heart lay the role of glutamate in Parkinson's. Elimination of mavoglurant means Addex's dipraglurant is now the only mGluR5-acting compound in development for LID, since Roche's RG7090 targets only depression and Fragile X.

Of course, it could be argued that this leaves the field clear for Addex, which after a major retrenchment is now focusing on orphan diseases and seeking a partner to take dipraglurant forward. Indeed, Novartis itself could now be a potential licensee, assuming that it remains interested in LID.

Unfortunately, this is far from certain, given the lack of progress with Novartis's other LID candidate, AQW051. A 71-patient phase II LID study was apparently completed this year, but the compound no longer appears in the group's R&D pipeline.

Still, Addex remains upbeat, and had earlier highlighted dipraglurant's effect on two aspects of dyskinesia – chorea as well as dystonia – and its immediate-release formulation, designed to mirror levodopa's pharmacokinetics. The Swiss biotech's stock is off 63% since the start of 2013.

Industry's shrinking levodopa-induced dyskinesia pipeline

Project	Mechanism	Company	Status	Detail	Trial ID
ADS-5102	Glutamate antagonist	Adamas	Phase II/III completed	83-pt study	NCT01397422
AVP-923	NMDA antagonist	Avanir	Phase II	16-pt crossover trial	NCT01767129
Dipraglurant	mGluR5 modulator	Addex	Available for licensing	83-pt phase II study completed	NCT01336088
Neu-120	NMDA receptor modulator	Neurim	Phase I/II	20-pt study completed	NCT00607451
Fipamezole	Alpha 2 adrenoreceptor antagonist	Santhera	Available for licensing	180-pt phase II completed	NCT00559871
Mavoglurant	mGluR5 modulator	Novartis	Discontinued	Lack of efficacy in phase II	NCT01491529
Safinamide	Dopamine reuptake inhibitor	Newron	No progress in LID	24-pt phase II completed	NCT01113320
AQW051	nAChRs alpha 7 agonist	Novartis	Discontinued	71-pt phase II completed	NCT01474421
NP002	nAChRs agonist	Neuraltus	Discontinued	65-pt phase I/II completed	NCT00957918
ND0611	Dopamine precursor	NeuroDerm	Discontinued	24-pt phase I/II completed	NCT01229332

Meanwhile, Newron Pharmaceuticals appears to have focused its dopamine reuptake inhibitor safinamide on boosting patients' "on" time as a levodopa add-on. An additional benefit in reducing LID would have been a big win, but this is no longer on the cards.

A 26-patient phase II study had tested safinamide specifically in LID, but no data were reported after it ended in 2011. Merck KGaA scrapped a licensing deal last year.

Huge scope?

Although with time LID becomes as debilitating as the underlying Parkinson's, levodopa has remained the mainstay treatment – largely because of the failure to develop anything better – the only concession being to wait as long as possible before

starting a patient on it (*Preladenant failure marks another Parkinson's pipeline disappointment, May 24, 2013*).

As such there is still scope for developing agents that might treat LID, allowing levodopa to be started earlier and continued for longer. This need continues to spur the handful of companies still working actively in this field, such as Avanir Pharmaceuticals and Adamas Pharmaceuticals.

Three days ago Avanir said it had enrolled the first patient into a small phase II trial of AVP-923, its dextromethorphan plus quinidine sulfate combination. Data, expected to inform AVP-923's further development in LID, are expected in the second half of next year.

Earlier this year Adamas reported positive results with its long-acting formulation of amantadine, ADS-5102, from the phase II/III Eased trial in LID. Both the 340mg and 420mg doses significantly improved Unified Dyskinesia Rating Scale total scores over eight weeks versus placebo, meeting the study's primary endpoint.

Beyond this, however, the pipeline is effectively dry, and those agents that have not suffered an obvious setback have languished with no development progress reported for several years.

Fipamezole, for instance, is still listed by the troubled Swiss firm Santhera as a licensing opportunity after completing a 180-patient phase II trial four years ago. However, former licensees that have already handed back to Santhera rights to the project include Ipsen, last year, and Biovail.

Given that levodopa will likely remain the standard Parkinson's treatment for some time yet, its nasty side effects are set to remain a major problem. As far as treating them, however, it has largely been a case of one step forward and two steps back.

To contact the writer of this story email Jacob Plieth in London at jacobp@epvantage.com or follow @JacobEPVantage on Twitter