In the search for improved Parkinson’s disease treatments, adenosine A2A receptor antagonists have been studied for a couple of decades now, without any success in terms of a product on the market. However, a few newer agents are now advancing through the clinic and this year the second candidate to enter final stage trials could well emerge (see table below).

The A2As offer the potential to improve on L-Dopa and other dopamine replacement therapies widely used to treat Parkinson’s. Whilst these therapies are fairly effective, their effects lessen with time and the side effects build, and it is hoped that the A2As can help overcome these drawbacks. However, it seems there is much work to be done before a success is seen in final stage trials, and a lack of big pharma interest in Parkinson’s disease more generally will probably not help the smaller companies involved find partners.

Progressive degeneration

In Parkinson’s disease progressive degeneration of certain nerve cells located in the brain causes a shortage of the neurotransmitter dopamine, causing motor symptoms such as slowness of movement, rigidity and tremors. Over time, L-Dopa gradually becomes less effective at controlling the symptoms, and starts to create its own problems.

After many years of use patients can experience dyskinesias, or uncontrollable jerky movements. Patients come to experience “off time”, when loss of motor control manifests itself, sometimes for several hours a day. Periods of good motor function are called “on time”.

In the brain, the adenosine A2A receptor regulates the release of dopamine. In Parkinson’s disease it is hoped that A2A inhibition can reverse motor symptoms and enhance the effect of L-Dopa, without inducing dyskinesias.

Most advanced

The candidate most studied has been instradefylline. Despite Roche abandoning development of the compound over a decade ago due to safety concerns, Kyowa Hakko Kirin is pushing ahead, in Japan only.

A phase III trial started last August in Japan in patients already taking L-Dopa. The study will examine the efficacy of two doses of the drug for reducing off time. Approximately 360 patients will be treated for 12 weeks, with a completion date of May 2011 pencilled in, with another study running concurrently to follow the patients for safety and efficacy measures over the longer term.

About five years ago the Japanese company conducted a similar series of phase III studies in the US and Europe, but received a non-approvable letter from the FDA in 2008. The regulator expressed concern about whether the efficacy findings supported clinical utility of the drug, and requested information about mineralisation in the brain, possibly the reason Roche had abandoned development beforehand.

As a result Kyowa decided to pursue development within Japan, and out-license the drug elsewhere, although it seems very unlikely that another partner can be found before more data is generated, if at all.

Mid stage

The remaining candidates are in mid-stage development.

Preladenant was inherited by Merck & Co from Schering-Plough, which completed dose finding phase II trials in late 2008. The large study enrolled 253 patients and found that “off” time was significantly reduced in the active arm, compared to placebo. Importantly, the “on” time was significantly increased without an increase in dyskinesias.

In late 2008 the company said it was preparing for a phase III study, but according to a www.clinicaltrials.gov another phase II is now underway, examining the effects of the drug on dyskinesia and Parkinsonism in
conjunction with intravenous levodopa infusion and oral carbidopa, another dopamine replacement therapy. The trial is supposed to finish next month.

The results from a long term safety study in patients who participated in the main phase II study are also awaited; the trial was due to complete late 2009.

The results from these two outstanding trials could well determine the path forward, if any, for preladenant, now that it has a new owner.

**Trials ongoing**

Meanwhile, Biogen Idec has been pushing its candidate, vipadenant, through phase II studies, with a number of phase I studies still ongoing. Partner Vernalis has said it hopes to see phase III studies started this year, although Biogen has not said much about the compound since March 2009, when it said it was in talks with regulators about the design of a phase III trial.

And lastly Synosia earlier this month presented results from a phase IIa study of its candidate, SYN-115, demonstrating a significant improvement in measures of motor and non-motor function in patients given the drug in combination with levodopa or alone.

As a private company, Synosia will no doubt seek a partner at some point, although without other successes elsewhere in the A2A pipeline in the meantime it could struggle.

Synosia bought rights to the drug from Roche in 2007 for development in selected indications of the central nervous system, under a broader deal over five drug candidates acquired from the pharma giant. The Swiss pharma giant has clearly decided that Parkinson’s is not an area of interest, and an analysis conducted by EP Vantage last year certainly supports the view that big pharma generally is not tempted by the indication, which has struggling to attract the sort of R&D investment that diseases such as Alzheimer’s has (Therapeutic focus - Parkinson’s disease in need of fresh impetus, February 6, 2009).

This view is supported by Barry Kenny of Heptares, which has a pre-clinical A2A available to license, but has found a number of companies interested in the candidate for its potential outside of Parkinson’s (EP Vantage Interview - Heptares seeking partner to back clinical work, April 22, 2010).

No doubt the fact that L-dopa is fairly effective and relatively cheap deters interest – a new drug would have to confer significant benefits to justify a premium price. However, the disease is predicted to afflict a rising number of the western world’s rapidly aging population in the coming years. So if a company can generate a real breakthrough, the market would certainly be there.

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