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NEWS IN BRIEF

Symptomatic AD treatment fails in first phase III

Lundbeck's and Otsuka Pharmaceutical's idalopirdine failed in a first phase III trial in patients with mild to moderate Alzheimer disease, further lowering expectations for a novel class of drugs that aim to offer symptomatic treatment for the neurodegenerative disease.

Idalopirdine is an antagonist of the 5-hydroxytryptamine receptor 5-HT_6, a receptor that is primarily expressed in areas of the brain that are involved in cognition and is thought to be involved in learning and memory (*Alzheimers Res. Ther.* **5**, 15; 2013). Despite a surge of interest in this target more than 10 years ago, the trial of idalopirdine is one of the first pivotal trials of a $5HT_6$-specific antagonist in Alzheimer disease. The partners have yet to release detailed data, but said the drug failed to meet the primary end point, a reduction in the Alzheimer Disease Assessment Scale-cognitive subscale (ADAS-cog) total score when treatment was added to acetylcholinesterase inhibitor donepezil.

Two more pivotal trials of the drug are ongoing, with data expected early next year.

Other companies who have also worked on this target include Pfizer and GlaxoSmithKline (GSK). Pfizer has discontinued two phase II candidates, in 2012 and then in 2015, due to lack of efficacy. GSK advanced its GSK742457 into phase II trials in 2005, but progress subsequently stalled. The biotech Axovant Sciences licensed and resurrected GSK's drug last year, renaming it RVT-101 and pushing it into phase III development.

Axovant has remained optimistic in the face of the recent failure, arguing that Lundbeck made changes between phase II and phase III trials — such as lowering the dosing of the drug — that could account for the lack of efficacy. Data from Axovant's phase III trial are expected next year.

Pfizer and Medivation's Dimebon (latrepirdine), once a highly hyped Alzheimer disease drug candidate, also has activity against the 5-HT_6 receptor, as well as against other targets including cholinesterase and *N*-methyl-D-aspartate (NMDA) receptors. The drug failed in phase III trials in 2011.

Asher Mullard

RNAi hits another rut

RNA interference (RNAi) company Alnylam Pharmaceuticals has discontinued one of its lead programmes, halting the development of phase III candidate revusiran due to an "imbalance of mortality". The discontinuation was a blow to the trailblazing RNAi company, re-raising concerns in some quarters about the future of RNAi platforms.

Alnylam's revusiran is a modified oligonucleotide conjugate that silences transthyretin (TTR) mRNA via the RNA-induced silencing complex (RISC). It was in phase III trials for hereditary ATTR amyloidosis with cardiomyopathy, a rare and life-threatening disease that is caused by the accumulation of misfolded TTR. Following reports of worsening peripheral neuropathy with the drug, the company unblinded the safety data: it found no evidence of drug-related neuropathy, but did find an increased risk of mortality.

The jury is now out on whether RNAi toxicity might affect Alnylam's entire platform. But, after assessing the safety of its other lead compound, patisiran, the company has decided to keep trials of this drug ongoing. Patisiran also silences TTR mRNA, and is in phase III trials for ATTR amyloidosis with polyneuropathy. Before the revusiran setback, Alnylam planned to file patisiran for FDA approval next year.

Key differences between patisiran and revusiran include the formulation and route of administration of the siRNA oligonucleotides. Subcutaneously administered revusiran consists of an siRNA that is conjugated to a *N*-acetylgalactosamine (GalNAc) ligand, using a first-generation chemistry. Intravenously administered patisiran consists of an siRNA that is encapsulated in a lipid nanoparticle. Alnylam has six other RNAi programmes in the clinic, all of which use a second-generation version of the GalNAc chemistry. The company has also licensed RNAi drugs to several partners.

RNAi-based companies have been on a roller-coaster ride over the past decade. Merck, Roche, Pfizer, Abbott and Novartis all invested heavily in the field, only to subsequently drop out. But Sanofi signed a US$700 million deal with Alnylam in 2014 for access to their technology, and Roche re-entered the space that same year with its acquisition of Santaris Pharma. In September, Amgen partnered with Arrowhead Pharmaceuticals to develop RNAi therapies for cardiovascular diseases.

Arrowhead Pharmaceuticals and Arbutus BioPharma also have siRNA-based drugs in the clinic.

Asher Mullard

Immuno-oncology drugs jostle for first-line setting

Merck's pembrolizumab has overtaken Bristol-Myers Squibb (BMS)'s nivolumab for the first-line treatment of non-small-cell lung cancer (NSCLC), shows data presented at the European Society for Medical Oncology (ESMO) meeting last month. But differences in trial design, and numerous ongoing trials of programmed cell death protein 1 (PD1) modulating antibodies paired with other drugs, mean that the fight for first-line settings has only just begun.

Merck tested its pembrolizumab in 305 patients with metastatic NSCLC and 'high' PD1 ligand 1 (PDL1) levels. Patients received either pembrolizumab as a monotherapy, or standard of care platinum-based chemotherapy. Pembrolizumab extended the progression-free survival by 4 months more than standard of care, impressing oncologists when the data were presented at ESMO and concurrently published in the *New England Journal of Medicine*.

BMS designed a broader trial with a lower PDL1 threshold, testing its nivolumab in 541 patients with advanced NSCLC and positive for PDL1 expression. Patients received either nivolumab as a monotherapy, or standard of care platinum-based chemotherapy. The trial failed on its primary end point, with nivolumab-treated patients averaging 1.7 fewer months of progression-free survival.

Shares in BMS plummeted over the summer when it announced the top-line data of its trial, wiping US$21 billion off the company's market capitalization as investors fretted over the loss of the first-line market. But, although Merck was a clear victor in this race for first-line dominance, its play-it-safe approach — to PDL1 expression and other factors such as lack of brain metastases, targetable mutations and prior steroid use — could limit roll-out of the drug. Merck's stringent patient-selection strategy would exclude approximately 90% of NSCLC patients in clinical practice, said Jean-Charles Soria, an oncologist at South-Paris University in France and a trial discussant at ESMO.

Further trials of PDL1 inhibitors in combination with other drugs, in NSCLC and other cancers, will yet determine the future of the first-line immunotherapy market.

Asher Mullard