NEWS IN BRIEF

FDA approval for Biogen's aducanumab sparks Alzheimer disease firestorm

The FDA has granted a controversial accelerated approval to Biogen's anti-amyloid antibody aducanumab. Despite a lack of evidence that the therapy improves cognitive outcomes, the FDA approved the antibody based on its ability to lower the level of amyloid plaques in the brain.

Just 2 years ago, aducanumab was destined for discontinuation. An interim analysis of two phase III trials suggested that these were unlikely to show cognitive benefit, and Biogen halted both trials. The company announced months later that a subgroup of patients in one of these trials showed signs of cognitive benefit. These data supported approval, said some investigators.

In an FDA advisory committee meeting in November, a panel of experts were highly critical of these results, and of Biogen's statistical methodology. Of 11 panellists, 10 voted that the data did not show that the drug was effective, a conclusion shared by some of the investigators on the aducanumab trials. The other panellist abstained.

Now, the FDA has approved the antibody via its accelerated approval pathway, deeming amyloid-β plaque reductions an approvable surrogate end point that is "reasonably likely to predict a clinical benefit". This end point has not been used before, and critics argue that the evidence does not, as yet, support it.

Biogen must run a confirmatory trial to see whether the anticipated benefit is real. It has yet to announce plans for this trial, and has up to 9 years to complete it. When the FDA grants accelerated approval to cancer drugs, it typically requires confirmatory trials to be underway at the time of approval.

Biogen will charge around US$56,000 per year for aducanumab. With around 6 million Alzheimer disease patients in the USA eligible for treatment, this creates a contentious path to mega-blockbuster status for this antibody.

Eli Lilly, Eisai and Roche have anti-amyloid antibodies in phase III trials. These too could soon be up for approval, if they lower amyloid levels in the brain. Some researchers fear that the approval will have unintended consequences, however, including complicating trials in Alzheimer disease, setting back interest in other targets and undermining regulatory standards.

Asher Mullard

Amgen overcomes historically undruggable target, with FDA nod for first KRAS inhibitor

The FDA has approved Amgen's sotorasib, a first-in-class KRAS-G12C inhibitor, for non-small-cell lung cancer (NSCLC).

The KRAS oncoprotein is mutated in up to 25% of cancers and carries a poor prognosis, but had long been considered undruggable. After researchers showed in *Nature* in 2013 that the KRAS-G12C variant had a druggable pocket, drug developers raced to advance candidates into the clinic.

The FDA's accelerated approval of sotorasib comes less than 3 years after Amgen moved the drug into trials. The nod was based on efficacy data from a subset of participants in the CodeBreaK 100 trial. The single-arm trial recruited 124 patients with $KRAS^{G12C}$-mutant NSCLC with disease progression after prior treatment. Amgen observed an overall response rate of 36%, and a median duration of response of 10 months. Common adverse events included diarrhoea, musculoskeletal pain and hepatotoxicity. 9% of patients discontinued treatment due to adverse events.

A phase III trial is underway to confirm these results. The FDA has also asked Amgen to explore lower doses of sotorasib, based on the possibility that the approved 960 mg dose represents a maximally tolerated dose rather than one that was optimized for both efficacy and safety. Oncologists have pointed to sotorasib as the latest example of the need to re-evaluate dose optimization strategies.

Analysts expect annual global sales of US$900 million for sotorasib by 2025, show consensus forecasts collected by Cortellis.

Other KRAS-G12C inhibitors are close behind. Mirati expects to file adagrasib for approval in NSCLC this year. But modest single-agent activity for KRAS-G12C inhibitors has refocused attention on combination strategies, in various cancers. Amgen is exploring 11 combinations, pairing sotorasib with agents including PD1/PDL1 blockers, MEK inhibitors and SHP2 inhibitors.

The druggability of the KRAS-G12C variant has renewed interest in other RAS-targeted approaches. Boehringer Ingelheim's SOS1 inhibitor BI-1701963 could have indirect activity across KRAS mutants. Moderna and Merck & Co.'s mRNA-5671 is a cancer vaccine that primes the immune system to hunt down cells that carry KRAS mutant neo-epitopes.

Asher Mullard

First approval of a complement C3 inhibitor opens up autoimmune and inflammatory opportunities

The FDA has approved Apellis Pharmaceuticals' complement protein C3 inhibitor pegcetacoplan for paroxysmal nocturnal haemoglobinuria (PNH). With this approval the pegylated cyclic peptide will now compete with Alexion/AstraZeneca's first-in-class blockbuster anti-C5 antibody eculizumab in this rare disease. But complement modulators could have activity in common diseases too.

"This is great news," says John Lambris, an immunologist at the University of Pennsylvania. Lambris discovered pegcetacoplan's parent molecule, and Apellis then licensed it. Despite speculation that sustained blockade of C3 might be unsafe because of C3's central role in innate immunity, this approval proves this is not the case, he adds.

PNH is a rare blood disorder in which uncontrolled complement activity kills red blood cells, causing life-threatening anaemia. The approval of pegcetacoplan was based on an 80-patient phase III trial of the drug versus eculizumab, in patients with low haemoglobin levels despite eculizumab treatment. Pegcetacoplan beat eculizumab on the primary end point, boosting haemoglobin levels by 3.84 g per deciliter compared with eculizumab at 16 weeks, investigators reported in the *New England Journal of Medicine*. With treatment in this trial, 85% of pegcetacoplan recipients no longer needed transfusions, up from 15% on eculizumab.

The most common serious adverse reaction on pegcetacoplan was infections. Like eculizumab, it carries a black box warning noting the risk of meningococcal infections.

Companies are working to expand the reach of complement-modulating agents. Apellis is developing pegcetacoplan for indications including rare kidney diseases called C3 glomerulopathies and amyotrophic lateral sclerosis. Amyndas Pharmaceuticals, founded by Lambris, is developing next-generation C3 inhibitors for periodontitis, ocular diseases and other diseases. Novartis and Roche/Ionis are in phase II trials with drugs that target complement factor B, a component of the alternative complement pathway. Sanofi is set to re-submit its anti-C1s antibody sutimlimab for approval in cold agglutinin disease.

"We're going to see a lot of activity here, especially if drug developers can succeed beyond the rare indications," says Lambris.

Asher Mullard