Therapeutic focus - A big year in store for antibodies in Alzheimer’s

Joanne Fagg

Baxter International’s decision to proceed with a second phase III trial of its immunoglobulin Gammagard in Alzheimer’s disease shows that there is still life in the late-stage pipeline for the degenerative condition (see table below). Since the failure in 2010 of Medivation’s Dimebon, Eli Lilly’s semagacestat and the Elan and Transition product ELND005, the space has gone mostly quiet as the next cohort of trials nears completion.

This year could be a big one for the antibody approach as both Eli Lilly’s solanezumab and Elan/Pfizer/Johnson & Johnson’s bapineuzumab are expected to report phase III data. As with Baxter’s blood product, both the antibodies target beta amyloid plaques in the brain, thought to be a hallmark of Alzheimer’s. Setbacks for the antibodies would likely raise further doubts about the peptide’s role in disease progression and would increase scepticism about the remaining candidates targeting that pathway (Therapeutic focus - What is plan B if A-beta Alzheimer’s hypothesis is void?, August 19, 2010).

Setbacks aplenty

Clinical setbacks have created a great deal of scepticism about progress in treating Alzheimer’s disease and dealmaking in the sector has ground nearly to a halt (Roche signs first Alzheimer’s deal of the year as crucial progress awaited, September 6, 2011). In a telling sign of pipeline struggles, amongst the late stage pipeline is a transdermal version of Aricept and a long-acting acetylcholinesterase inhibitor in the form of Luye Pharma’s Huperzine A.

The condition, while affecting a growing number of older people as life expectancy increases, has proven stubborn to treat – the marketed products, mostly acetylcholinesterase inhibitors and NMDA antagonists, have shown modest efficacy in slowing the progression of the disease. Thus, a truly disease modifying treatment is sought.

Much research has focused on beta amyloid plaques in the brain. Beta amyloid is a fragment of the amyloid precursor protein, which in healthy brains is broken down and eliminated. In Alzheimer’s disease patients, they form deposits that are thought to contribute to the degradation of brain cells.

The road more travelled

Illinois-based Baxter announced it was initiating the second phase III trial of Gammagard following the news that its first late-stage trial had passed an interim futility analysis. That first trial in 390 patients is likely to report data early next year.

Gammagard is a human immunoglobulin product now used to treat primary immunodeficiency. As it contains antibodies to beta amyloid, the hope is that by boosting the antibody count Gammagard can inhibit beta amyloid’s neurotoxic effects.

As analysts from Bryan Garnier note, success for Gammagard might also spur off-label use of other human immunoglobins, such as Grifols’ Flebogamma and Gamunex.

Following a similar theory, the monoclonal antibodies solanezumab and bapineuzumab bind to beta amyloid and, it is hoped, prevent the build up of deposits in the brain.

The first news is expected from Lilly’s solanezumab: its two clinical trials are expected to report in the third quarter, and word on a futility analysis could come as early as next week during its fourth quarter earnings call. Bapineuzumab, the Elan product to be co-marketed by J&J and Pfizer, is also expected to report data toward the end of 2012. A great deal of scepticism surrounds both products.

Analysts from Morgan Stanley make a flat prediction of failure for the Lilly molecule and forecast share price softness following that failure – blood levels of beta amyloid increased in phase II, which Lilly management said
was inactive because of antibody binding. If it succeeds, EvaluatePharma’s consensus forecasts sales of $299m in 2016, a number that will be highly risk adjusted and not reflect the drug’s true potential should it succeed.

Meanwhile Cowen analysts suggest that bapineuzumab, Elan’s next key catalyst, may succeed in showing efficacy on biomarker endpoints but fail to improve functional measures sufficiently to win regulatory approval.

In either case, the milder patients with less disease progression may be the most promising population – beta amyloid binding may only be successful in preventing the formation of plaques, not their elimination.

**Reading across**

It would be difficult for failure of the two monoclonal antibodies not to have some read across to most the remaining phase III pipeline – significantly, the failure of the engineered antibodies should have huge implications for the natural antibodies contained in Gammagard.

Likewise, SK Holdings’ SK-PC-B70M is known to reduce beta amyloid blood levels and plaque in preclinical rat models, but not much information is available on its human trials. A phase III trial is ongoing, with completion listed in May.

The remaining phase III product relies neither on the beta amyloid hypothesis nor on repurposing acetylcholinesterase inhibitors. It is Accera’s AC-1204; the privately held company believes the agent provides ketone bodies that brain cells with defective glucose metabolism can use as an alternative fuel. The company already markets Axona as a medical food for metabolism in Alzheimer’s patients. The listing at clinicaltrials.gov suggests completion in mid-2013.

It is likely that 2012 will be the one in which beta amyloid will be proven or dismissed as a useful target in fighting Alzheimer’s disease. If doubts are borne out, new strategies are being tested in phase II, but that will push hopes for a new disease modifying treatment several years into the future.

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