J&J’s billion dollar punt on anti-amyloid antibody

Johnson & Johnson’s $1.5 billion deal with Elan provides the latest validation of bapineuzumab’s commercial potential in Alzheimer’s disease. The partnership not only highlights the flagship program targeting beta amyloid, but also neatly pulls Dublin-based Elan out of a financial tailspin (Box 1). But for the Alzheimer’s field as a whole, the success or failure of bapineuzumab will likely have broader implications for the future direction of drug development.

The bapineuzumab development program will be run out of a newly formed company, which will acquire Elan’s assets and rights related to Alzheimer’s program with Wyeth (now Pfizer). The program aims to recruit about 3,600 patients and represents the single most exacting test of the so-called amyloid hypothesis, which defines the accumulation of beta amyloid and its deposition in plaques in the brain as the key pathological process driving Alzheimer’s disease.

Clearing existing beta amyloid deposits from the brain, or hindering their formation, is the paradigm driving the vast majority of the Alzheimer’s development programs currently underway (Table 1). The dominant view is that other processes, including the formation of neurofibrillary tangles of hyperphosphorylated tau—another pathological hallmark of Alzheimer’s—occur downstream from beta amyloid plaque formation.

Even if bapineuzumab fails, however, that basic thesis will not disappear, for other factors could be invoked to explain its downfall. “You’re never quite sure whether you’re testing the hypothesis or testing the molecule, because you have to do both at once,” says Eric Siemers, medical director of Alzheimer’s research at Eli Lilly, of Indianapolis.

But a negative result would be a significant setback for the field, after the recent failures of two other anti-amyloid drugs, the gamma secretase inhibitor Flurizan (R-flurbiprofen) and Alzhemed (tramiprosate), which were being developed by Myriad Genetics, of Salt Lake City, Utah, and Laval, Canada–based Neurochem (now Bellus Health), respectively. Neither failure implicated the basic goal of inhibiting beta amyloid formation or deposition. Flurizan, which prevents beta amyloid formation by inhibiting the cleavage of amyloid precursor protein into beta amyloid peptide, failed to achieve a sufficiently efficacious concentration in the brain. Alzhemed, a glycosaminoglycan mimetic, was designed to prevent beta amyloid aggregation. Here, though, “the preclinical evidence was not very strong,” says Dennis Selkoe, professor of neurologic diseases at Brigham and Women’s Hospital in Boston, who recently stepped down

Elan’s recently revamped manufacturing and research facilities in Athlone, Ireland.
from Elan’s board but remains a scientific consultant to the company.

Expectations surrounding the bapineuzumab trial have been tempered by its performance to date. It failed to demonstrate statistically significant efficacy in a phase 2 trial, although it did work in a subgroup of patients: noncarriers of the Apolipoprotein E4 (ApoE4) allele, a known genetic risk factor for Alzheimer’s. “It will not be a home run. It may be a double. I hope it’s not only a single, but if a single is evidence of disease modification that might be good news,” says Selkoe, who was a founder of Athena Neurosciences, the San Francisco–based firm acquired by Elan in 1996 and was a director of the latter company until mid-July.

Ian Sanderson, analyst at Cowen in New York, gives bapineuzumab a 50% likelihood of reaching the market, based on clinician surveys conducted by the investment bank. “The phase 3 trial, while very robust in terms of patient numbers, arguably has the doses wrong,” he says. None of the studies is testing a dose below 0.5 mg/kg, which was the most effective dose in the phase 2 study. “The optimal dose may be somewhere between 0.15 mg/kg and 0.5 mg/kg, but it’s difficult to tell,” he says. On bapineuzumab’s chances, J&J spokesperson Srikant Ramaswami says: “I’m not going to speculate about what analysts or anybody else are saying about this - we believe this represents a significant opportunity for us.”

It could be late 2011 before the data become available. “They’re frankly having trouble enrolling the largest component [of patients], which is the ApoE4 noncarriers,” Sanderson says. Clinical investigators generally find noncarriers harder to access, he says, as carriers of the ApoE4 allele—a known genetic risk factor for Alzheimer’s—are more usually treated at academic medical centers. The incidence of vasogenic edema (fluid build-up in the brain) that was observed in the phase 2 program, although low, particularly in noncarriers, may be at issue. “The risk-reward [benefit] is a little bit skewed in patients’ minds,” Sanderson says.

A key issue for all Alzheimer’s drugs is the status of patients who are recruited into trials of new therapies. Most have mild-to-moderate disease, and it may be too late to undo the damage at that stage. Starting patients earlier, particularly those with a known genetic risk, is becoming a more realistic prospect, however. “That’s going to start soon. There have been many discussions,” Selkoe says. The Dominantly Inherited Alzheimer’s Network, led by John Morris at Washington University in St. Louis, is coordinating one such initiative. “Within families [genetically predisposed to Alzheimer’s], the age at onset is fairly tight, and presymptomatic genetic prediction is reliable. That might be the setting in which efficacy of antiamyloid therapy is most likely to be demonstrable,” says Sam Gandy, professor of neurology and psychiatry at Mount Sinai School of Medicine in New York.

In the meantime, several other phase 3 programs are edging closer to conclusion. After bapineuzumab, Lilly’s solanezumab is the next most advanced anti–beta amyloid antibody. It has a subtly different mechanism of action. “Our antibody only binds to soluble Abeta [beta amyloid] monomers. So it does not bind directly to the plaques,” Lilly’s Siemens says. Although beta amyloid monomers are themselves not considered to be toxic to neurons, depleting these monomers in solution may mobilize plaque-bound beta amyloid into solution, he says. Recent work, by Selkoe’s lab and other groups, have demonstrated that various oligomers, including dimers, are synaptotoxic. Second- or third-generation therapies could conceivably be designed to target these species. But Selkoe is skeptical: “frankly speaking I do not think that’s necessary,” he says.

Lilly is also developing the industry’s most advanced gamma-secretase inhibitor, semagacestat, which progressed to phase 3 trials on the basis of biomarker, rather than efficacy, data. Drugs in this class carry a danger of inhibiting Notch signaling, which is involved in multiple cellular control processes. “From a practical standpoint, we’re not seeing this as a major problem in these studies,” Siemens says.

“The word on that is it’s probably not going to show efficacy because they’re dosing it for...
Box 1 Saving Elan

The Johnson & Johnson (J&J; New Brunswick, New Jersey, USA) deal is a life preserver for Elan, which has been in financial trouble since last summer, when it revealed that the phase 2 trial of bapineuzumab (AAB-001) had missed its primary endpoints, albeit with some efficacy in certain patient subgroups. Days later, Elan also announced that two more patients taking its multiple sclerosis drug Tysabri (natalizumab) had contracted the potentially fatal brain disease progressive multifocal leukoencephalopathy. These events combined to drive down Elan’s stock from more than $33 last summer to less than $10, where it still languishes today.

Elan ended 2008 with about $375 million in cash and equivalents. With the summer’s bad news still hanging around its neck (and stock price) and expecting to spend around $350 million in R&D this year, the company needed to hunker down. In January, it hired Citigroup to review “strategic alternatives,” including a merger or an outright sale of the company. In the first quarter, it closed offices in New York and Tokyo. In February, it also cut 230 positions (~14% of the total workforce), including research and clinical development positions, and looked to further curtail spending by saying it would “reassess” investing in a biologics manufacturing facility and suspending fill-finish activities in preparation for launching bapineuzumab until after the phase 3 results are known.

Despite these savings, Elan has still been wrestling with how to pay for its promising—though expensive—lead product in Alzheimer’s. Last year, Elan spent $113 million on its Alzheimer’s Immunotherapy Program (AIP), partnered with Wyeth (in the process of being purchased by Pfizer), and estimated it would spend as much as $500 million on bapineuzumab and the rest of the portfolio over the next three or four years. This was looking more and more impossible for Elan, given its dwindling cash position and a troubling net debt of $1.4 billion.

The J&J deal solves both problems. First, J&J takes over the AIP, which includes the intravenous formulation of bapineuzumab, as well as a subcutaneous version and an Alzheimer’s vaccine (AAB-001), in phase 2 development. J&J will build a new joint venture around AIP and own 51.1% of it (with Elan holding the rest), and J&J will dump up to $500 million into development, thus relieving Elan of about $100 million in annual R&D expenditure. Second, J&J invested $1 billion into Elan itself, receiving about 18.4% of Elan’s outstanding shares in return—making it the largest shareholder. This influx of cash will allow Elan to reduce its net debt by 70%, to $400 million. Elan believes that the reduction in R&D spending, coupled with an expected growth in Tysabri sales, will allow the firm to post a pre-tax profit and be cash-flow positive by the end of 2010.

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