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Product Discovery & Development

Waiting for mAbs in AD

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The next set of Phase III data in Alzheimer's disease will come next year from therapeutic antibodies against beta amyloid. Safety issues have dogged bapineuzumab from **Johnson & Johnson**'s Janssen Alzheimer Immunotherapy unit and partner **Pfizer Inc.**, but new data suggest vascular complications can be mitigated with lower dosing.

Bapineuzumab hit a speed bump in 2009 when imaging studies in Phase II trials revealed vascular abnormalities collectively termed vasogenic edema in the brains of a small number of patients receiving high doses.

A 78-week open-label extension of the Phase II trial and a reanalysis of brain scans from previous Phase II trials suggest there were more of these vascular abnormalities than previously thought, but they spontaneously cleared when dosing was suspended.

Among the 194 patients in the extension trial who received 0.15 mg/kg, 0.5 mg/kg and 1.0 mg/kg bapineuzumab every 13 weeks for an average of 2.6 years, 9.3% developed vascular abnormalities.

The reanalysis of brain scans of 262 participants in previous Phase II trials revealed 36 cases of imaging abnormalities suggestive of vasogenic edema, including 15 cases that had not been detected during the trials.

In all cases, the abnormalities resolved after temporary dosing suspension and subsequent shift to a lower dose.

Reisa Sperling, associate professor of neurology at **Harvard Medical School**, presented the reanalysis at the **Alzheimer's Association** International Conference (AAIC) in July. She concluded that vasogenic edema, which she and Janssen have renamed amyloid-related imaging abnormalities-edema/effusions (ARIA-E), is more common at baseline than previously thought.

The first of four ongoing Phase III trials of bapineuzumab will be completed in mid-2012. Primary endpoints are cognitive and functional measurements. Janssen is using PET imaging to monitor brain amyloid levels and to detect vascular abnormalities.

Eli Lilly and Co.'s solanezumab also is in two large Phase III trials — EXPEDITION and EXPEDITION2 — in which over 2,000 patients receive monthly injections of 400 mg of solanezumab or placebo for 18 months.

Lilly is monitoring cognitive endpoints, CSF biomarkers and brain amyloid levels using Amyvid florebetapir (18F-AV-45), an imaging reagent acquired through the purchase of Avid Radiopharmaceuticals Inc. last year. Top-line data are expected in late 2012.

Eric Siemers, senior medical director at Lilly, said so far no more than 1% of patients treated with solanezumab have developed vasogenic edema in Phase II and Phase III trials, about the same rate seen in baseline brain scans.

Siemers suspects the difference in vasogenic edema rates between bapineuzumab and solanezumab could be a consequence of the different mechanisms of action.

Vasogenic edema is thought to arise from the accumulation of mAb-antigen complexes in the brain vasculature.

Bapineuzumab binds to aggregated beta amyloid, which is found primarily in the brain, while solanezumab binds to monomeric beta amyloid, found throughout the body.

Thus, one possibility is that bapineuzumab bound to large beta amyloid aggregates might be more prone to getting stuck in the brain's blood vessels than a smaller complex of solanezumab and monomeric beta amyloid.

Meanwhile, **Baxter International Inc.** is running a Phase III

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program for Gammagard Liquid 10%, a formulation of human plasma-derived IgG antibodies.

Gammagard contains a broad range of naturally occurring antibodies, including ones that target beta amyloid, and is marketed to treat primary immunodeficiency.

David Gelmont, senior director at Baxter Biosciences, said the precise mechanism of Gammagard's action in AD is unknown, but may involve immunodepletion of peripheral beta amyloid by anti-beta amyloid antibodies that occur naturally in human serum.

The primary endpoints are cognitive; secondary endpoints are quality of life assessments and MRI brain volumetrics.

Data from two Phase III trials — the Gammaglobulin Alzheimer's Partnership (GAP) study, which started in 2008, and a 72-week trial that will start this year — are expected in 2013.

COMPANIES AND INSTITUTIONS MENTIONED

Alzheimer's Association, Chicago, Ill.
Baxter International Inc. (NYSE:BAX), Deerfield, Ill.
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Harvard Medical School, Boston, Mass.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Pfizer Inc. (NYSE:PFE), New York, N.Y.

AD pipeline: Immunotherapies

At least 14 immunotherapeutics or vaccines against beta amyloid are in clinical development to treat Alzheimer's disease (AD). Three Phase III antibodies that are thought to neutralize beta amyloid are expected to yield data in 2013. *Source: BCIQ: BioCentury Online Intelligence*

Company	Product	Description	Status
Baxter International Inc. (NYSE:BAX)	Gammagard Liquid 10%	Plasma-based therapy containing IgG antibodies	Ph III
Eli Lilly and Co. (NYSE:LLY)	Solanezumab (LY2062430)	Antibody binding to soluble beta amyloid	Ph III
Johnson & Johnson (NYSE:JNJ)/ **Pfizer Inc.** (NYSE:PFE)	Bapineuzumab (AAB-001)	Humanized mAb against beta amyloid	Ph III
AC Immune S.A./Genentech Inc./ Roche (SIX:ROG; OTCQX:RHHBY)	Anti-Abeta (RG7412)	Humanized mAb against beta amyloid	Ph II
Affiris AG/GlaxoSmithKline plc (LSE:GSK; NYSE:GSK)	AD02	Vaccine against beta amyloid	Ph II
Cytos Biotechnology AG (SIX:CYTN)/ **Novartis AG** (NYSE:NVS; SIX:NOVN)	CAD106	Vaccine against beta amyloid	Ph II
Johnson & Johnson (NYSE:JNJ)/ **Pfizer Inc.** (NYSE:PFE)	PF-5236806 (ACC-001)	Beta amyloid-related immunotherapeutic conjugate	Ph II
MorphoSys AG (Xetra:MOR)/ **Roche** (SIX:ROG; OTCQX:RHHBY)	Gantenerumab (RG1450)	HuCAL-derived human mAb targeting amyloid beta	Ph II
AC Immune S.A.	ACI-24	Vaccine that stimulates the production of beta sheet conformation-specific antibodies	Ph I/II
Affiris AG/ GlaxoSmithKline plc (LSE:GSK; NYSE:GSK)	AD01	Vaccine against beta amyloid	Ph I
Affiris AG / GlaxoSmithKline plc (LSE:GSK; NYSE:GSK)	AD03	Vaccine against beta amyloid	Ph I
BioArctic Neuroscience AB/ Eisai Co Ltd. (Tokyo:4523; Osaka:4523)	BAN2401	Humanized conformational specific mAb targeting the toxic beta amyloid protofibrils	Ph I
GlaxoSmithKline plc (LSE:GSK)	GSK933776	mAb against beta amyloid	Ph I
Pfizer Inc. (NYSE:PFE)	PF-5236812 (AAB-003)	Humanized 3D6 full length light chain antibody	Ph I