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By Lynne Peterson

SUMMARY

No significant new drug for Alzheimer's Disease is likely to be approved by the FDA for at least three to five years. ♦ NeuroChem's Alzhemed is in Phase III trials but probably is at least three years away. ♦ Elan's monoclonal antibody AAB-001 is in Phase I trials, and Elan's new vaccine (immunoconjugate) is still in preclinical development. ♦ Gamma and beta secretase inhibitors are in early development, with a long and uncertain road ahead, and doctors are skeptical about Prana's metal chelator, clioquinol. ♦ Forest Laboratories' Namenda is performing much as doctors expected, and they predicted usage would increase. ♦ Despite questions about the benefit and cost-effectiveness of acetyl-cholinesterase inhibitors (AChEIs), doctors have not cut back on their use for AD – yet – and off-label use is increasing in mild cognitive impairment. ♦ It appears that all atypical antipsychotics are not equal in treating behavior problems in AD patients; AstraZeneca's Seroquel and Bristol-Myers Squibb's Abilify may have a better profile.

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THE ALZHEIMER'S ASSOCIATION'S 9TH INTERNATIONAL CONFERENCE ON ALZHEIMER'S DISEASE AND RELATED DISORDERS (ICAD)

Philadelphia, PA
July 17-22, 2004

Alzheimer's Disease (AD) affects about 4.5 million Americans, and there is tremendous demand for new drugs to treat the disease. Unfortunately, it is likely to be at least three to five years before any significant new drug is approved by the FDA. NeuroChem's Alzhemed, which is in Phase III trials, may be closest, but it is not likely to be approved before 2007, Elan's monoclonal antibody AAB-001 is only in Phase I trials, and Elan's new vaccine (immunoconjugate) is still in preclinical development. The gamma and beta secretase inhibitors also are still in early development, with a long and uncertain road ahead. An expert said, "The fundamental problem is that we have already picked the low hanging fruit."

However, some drugs could come from behind, leapfrogging over the apparent front-runners. An expert warned, "There are drugs in trials outside the U.S. that may surprise people."

Many Alzheimer's patients are not diagnosed – or treated – in the early stages of the disease, and many late-stage patients are not treated either. At a symposium, sponsored by Forest Laboratories, these issues were discussed – and the discussion was videotaped for later use in educating primary care doctors about the diagnosis and treatment of Alzheimer's Disease. Among the points the panelists made were:

- **There are many reasons families and doctors fail to diagnose AD.** A U.K. doctor commented, "In Europe, many times doctors don't see an added value of making the diagnosis of Alzheimer's Disease." A U.S. doctor added, "Families also sometimes fail to recognize the dementia syndrome…So, it is not just clinicians who fail to diagnose." A third expert said, "Sometimes patients and the family hide the diagnosis because they are afraid that driving privileges will be revoked or the person will be put in a nursing home…And for doctors, the diagnosis opens a Pandora's box – with a lot of work to be done counseling families, planning, discussing drug and non-drug interventions – that they may not wish to do that." A fourth expert said, "Doctors need to spend more time, to speak to the family, to at least do a simple test – like the MMSE – and a few blood tests. I also strongly recommend either an MRI or a CT scan."
- **Acetylcholinesterase inhibitors are modestly beneficial.**
- **There is a bias against treating AD patients in nursing homes,** but drug therapy can be beneficial even in patients with very severe AD. A speaker said, "If you get a point or two of MMSE in someone with severe AD, it makes very little difference, but if they function better or have fewer behavior problems, that is good." Another doctor said, "Whatever stage the patient is, there are things that can be done to make their life better."

➢ **Combining Forest's Namenda (memantine) and an AChEI might improve the tolerability of the AChEI.**

The economic costs of Alzheimer's Disease have been estimated to be about $30,000-$40,000 per year per patient, but an economist from the University of Pennsylvania did a new analysis that puts the costs much lower. He said, "We believe our study is a more nationally representative sample – where not everyone gets care…Our estimate for a newly diagnosed woman…is that she will live about six years and will cost $100,000-$110,000 and a man will cost $40,000-$50,000 less…Only 5% of patients are alive 15 years after diagnosis…What does this mean?...We need an effective drug or therapy that is reasonably priced. We've done work that says that if you are slowing disease by six months or a year, you won't save money…We need a drug that slows disease for several years before we see a savings. One or two years is not enough."

Genomic studies may help shed light on AD. GlaxoSmithKline is conducting major genomic studies in AD, Parkinson's Disease, ALS, depression, and possibly schizophrenia. One major study, GENADA, is being conducted primarily in Canada and will compare 1,000 controls to 1,000 dementia patients, doing blood and DNA screens. Recruitment for the first phase is complete, and the patients will be followed for another couple of years clinically to see if genomic phenotypes match the clinical features. Glaxo also is doing SNPs on the adverse events in these patients. A second, similar study is being conducted by Glaxo in Cardiff, England, with 500 AD patients and 500 controls.

ACETYLCHOLINESTERASE INHIBITORS (AChEIs)

Nearly a quarter of diagnosed AD patients take one of the AChEIs. Off-label use of AChEIs in mild cognitive impairment (MCI) is increasing, but two negative studies of Pfizer's Aricept (donepezil) could cause a slowdown in use of Aricept and perhaps other acetylcholinesterase inhibitors in AD. A Pennsylvania doctor said, "I probably will start prescribing AChEIs earlier…There's no real downside, and patients often want them."

Marketed AChEIs

Manufacturer	Brand Name	Generic Name
First Horizon	Cognex	Tacrine
Johnson & Johnson	Reminyl	Galantamine
Novartis	Exelon	Rivastigmine
Pfizer	Aricept	Donepezil

AXONYX'S Phenserine

There was no new data at this meeting on phenserine, an AChEI with a dual mechanism of activity that gives the company hope that it will slow progression of AD as well as improve memory and cognition. Few sources were even aware of it. One expert who did know something about it commented, "I'm modestly skeptical about the effect of progression."

JOHNSON & JOHNSON'S Reminyl (galantamine)

A researcher presented the results of a Phase III study of a new, once-daily formulation – galantamine PRC. The study found galantamine PRC:

- Was effective in mild-to-moderate AD.
- Had a similar clinical profile to the immediate-release formulation.
- Has a potential tolerability advantage.

NOVARTIS'S Exelon (rivastigmine)

Data was presented from the 541-patient, randomized, double-blind, placebo-controlled EXPRESS trial, indicating Exelon is effective in treating dementia associated with Parkinson's Disease (PD), which occurs in about 40% of PD patients. Researchers concluded:

- A mean dose of 8.7 mg/day produced significant improvements across a wide range of symptoms in all key domains.
- The effect size was similar to that observed in AD patients in earlier trials.
- The drug was generally well tolerated.

EXPRESS Trial Results

Measurement	Exelon n=362	Placebo n=179	p-value
Completers	72.7%	82.1%	---
Primary endpoint #1: ADAS-cog	+2.1	-0.7	.001
Primary endpoint #2: ADCS-cgic	3.8	4.3	.007
Adverse events	83.4%	70.4%	---
Nausea	29.0%	11.2%	---
Vomiting	16.6%	1.7%	---
Tremor	9.9%	3.9%	---

A Novartis source also said the company is working on:

- An Exelon patch.
- An AD vaccine.

PFIZER'S Aricept (donepezil)

Doctors at this meeting have been talking about a three-year study reported in a June 2004 issue of ***The Lancet*** which found that Pfizer's Aricept does not delay the onset of disability or the need for placement in a nursing home in patients with mild-to-moderate Alzheimer's. The researchers concluded Aricept has little overall benefit and is not cost

effective. An expert said, "Patients shouldn't stop taking the AChEIs because they could decline coming off of them. They may not prevent nursing home admissions, but they do provide symptom relief."

Will this report cause American use of Aricept or AChEIs in general to go down? Experts doubt it, but they aren't sure. One said, "I don't think use will go down. I think doctors will counsel patients, but it could have a negative impact." Another expert said, "It will have an impact because patients only read the headlines. A number of my patients called or wrote to ask about this, but they all stayed on Aricept after I talked with them…The biggest impact could be with payers – if payers have the power to withdraw payment for an approved treatment." A third source said, "***The Lancet*** article showed you can stop and restart an AChEI to see if it is working – if patients will allow that, but a lot of families won't allow it…Because Aricept is so safe, there is no real need to withdraw it. In the future I may do more stop and start, and the study gives some more data to use when families resist that approach."

However, a second negative Aricept report was released at this meeting. Data from a clinical 769-patient study in amnesic mild cognitive impairment (MCI) reported disappointing results. At three years, there was no statistically significant difference in the primary endpoint (progression to clinically defined Alzheimer's Disease) with either vitamin E or Aricept vs. placebo. The progression curves for placebo and vitamin E were virtually identical at all time points. Aricept patients appeared to have a progression benefit compared to placebo – but only during the first 18 months. By 36 months, the Aricept patients "caught up" with the decline in vitamin E and placebo patients. The dropout rate in this trial was 13% overall per year, with slightly more dropouts early.

Progression to Clinically-Defined Alzheimer's Disease

Time period	Placebo n=259	Aricept 10 mg/day n=253	Vitamin E 2000 IU/day n=257	Total
6 months	17%	2%*	8%	27%
12 months	21%	14%*	25%	60%
18 months	16%	14%*	17%	47%
24 months	8%	14%	13%	35%
30 months	6%	8%	7%	21%
36 months	5%	11%	6%	22%
Number of patients who converted from MCI to AD	73	63	76	---
Mean time to conversion	484 days	661 days	540 days	---

*p<.05 vs. placebo

Researchers concluded:

- Neither Aricept nor vitamin E reduced progression to Alzheimer's Disease over 36 months.
- Aricept appeared to reduce the risk of progression for up to 18 months. Dr. Ronald Petersen of the Mayo Clinic, the principal investigator, said the reason is not clear why the benefit ceases at 18 months, "That is the million dollar question...It is uncertain whether the drug has a modest effect over a period of time and then the underlying degenerative process overwhelms the drug effect at that time…or whether the chemical effect of the drug just lasts for a period of time."
- Aricept had an effect on overall function, memory, and language for up to 18 months.
- Amnesic MCI strongly predicted progression to AD.

Asked how these findings compare to ***The Lancet*** report which found little value to Aricept, Dr. Petersen said, "These findings are not inconsistent with ***The Lancet***, which was talking about long-term nursing home placement…We are saying the drug (Aricept) has a symptomatic effect perhaps for a period of months, and that is still important. Nevertheless, I think the symptomatic effect may be important, certainly on an individual patient basis, and statistically on a group basis." Dr. Petersen also said the data is still being analyzed, so it is too early to make clinical recommendations. He explained, "We are stopping short of making any clinical recommendations at this time…Vitamin E doesn't look promising but we are not making any recommendations now…I can't say we should treat (with Aricept) for a certain period and stop. That is an individual doctor/patient decision…What's important is that we can intervene at the pre-AD stage and have an impact. This is not prevention, but it is symptom alteration." He said that investigators will meet in early September 2004 for a roundtable discussion of the findings.

NEW ALZHEIMER'S THERAPIES IN DEVELOPMENT

Statins: MERCK'S Zocor (simvastatin) and PFIZER'S Lipitor (atorvastatin)

Researchers have been attempting to determine whether statins are an effective preventive therapy for Alzheimer's Disease, but they still don't have an answer.

- A University of Alabama at Birmingham researcher reported that Zocor helps mice with memory problems regain their ability to navigate mazes.
- Swedish researchers reported that statins have mixed effects on marker molecules in blood and spinal fluid that may track the severity of Alzheimer's Disease.
- A Duke University researcher analyzed all existing randomized controlled trials of statins in people without dementia (>30,000 people) and found no evidence that any statin protects against cognitive decline.
- A second Duke study of a small group of elderly people at risk for dementia found that the rate of brain tissue shrinkage (by MRI) was no different between statin users and non-users.

- A U.K. study found that four different statins reduce, to a varying extent, brain cell production of a protein fragment thought to play a key role in Alzheimer's, with Novartis's Lescol (fluvastatin) the most effective. Initially, the drugs all increase the amount of the fragment released by cells, but long-term use of statins in patients would lead to a decrease in the overall amount released.

Dr. John Breitner of the University of Washington suggested that this new data argues against the use of statins for Alzheimer prevention. He said, "If you look at a 'snapshot' of statin users compared with non-users at a single moment in time, statin users seem to have a lower risk of Alzheimer's…But if you…follow (people) over several years, the benefit of statins in warding off dementia largely disappears."

Several large-scale clinical trials currently underway to determine the benefit of statins in Alzheimer's, including:

- CLASP, sponsored by the National Institute on Aging (NIA), is investigating the safety and effectiveness of Zocor to slow the progression of Alzheimer's. This two-year, Phase III study is investigating whether Zocor can slow the progression of AD.
- A study sponsored by the National Institute of Mental Health (NIMH) on the short-term use of either Merck's Mevacor or ibuprofen on levels of beta amyloid in people at risk for developing Alzheimer's.
- LEADe, a Pfizer-sponsored study of the safety and efficacy of Lipitor in combination with Aricept in patients with mild-to-moderate Alzheimer's.

Gamma and Beta Secretase Inhibitors

Several companies – including Lilly, Merck, and Pfizer – are working on secretase inhibitors. No beta secretase (BACE-1) inhibitors are currently in human clinical trials, but one gamma secretase (Lilly's LY-450139) is in Phase II development.

Some general research posters were presented that help to evaluate the secretase inhibitors, including:

- One poster concluded that "caution may be necessary when targeting BACE-1 (beta secretase) for the treatment of Alzheimer's Disease." The concern is that inhibiting beta secretase in mice can cause anxiety and memory deficits. A German researcher, commenting on these findings, said, "You need to be a little less afraid (of inhibiting beta secretase) than the data suggests because Alzheimer's patients are older, so the effect may be less. There is a need to have an inducible knockout mouse to test this…We still don't understand the biological function of beta secretase."
- Another poster found: "Normal gamma secretase cleavage mainly produces $A\beta_{1\text{-}42}$, which suggests abnormal Aβ processing in all disease cases with a large increase in $A\beta_{1\text{-}40}$…$A\beta_{1\text{-}40}$ may be a better indication of degeneration and toxicity than $A\beta_{1\text{-}42}$."

Yet, there is debate among experts about the role of beta amyloid in AD. One doctor said, "I am not a great fan of the amyloid hypothesis…I personally don't think it is the primary event." Another commented, "Side effects are still a concern with both beta and gamma secretases." A third expert said, "The problem with the amyloids is a lack of certainty as to what extent a change in amyloid has on clinical impact. There are patients with a lot of amyloid and no dementia, and vice versa. There is no question that amyloid is a part of the disease, but we don't know where it comes into the picture. If you eliminate amyloid but leave behind dementia, what market is there for that? My guess is that eliminating Aβ will help some segment but won't be a panacea."

ELAN

Elan has at least four Alzheimer's agents in its portfolio. An expert suggested that Elan could accelerate its development program with recruiting strategies:

1. **AN-1792**, the original vaccine. Development was halted due to adverse events, but new data from the AN-1792 Phase IIa trial was presented at this meeting. This trial was a double-blind, placebo-controlled study of 372 patients with mild-to-moderate AD, with a 4:1 randomization. Dosing was halted in January 2002 after reports of encephalitis and deaths in some patients. However, the trial remained blinded, and patients continued to be followed. The patients who continued in the trial did not show a statistically significant improvement in the primary cognitive endpoints at 12 months vs. placebo, but there was an improvement in a composite neuropsychological performance measure which included the memory component.

An Elan official insisted AN-1792 is not going forward in development. At the American Academy of Neurology meeting in 2003, doctors suggested that the vaccine might be able to be given if any inflammation was treated with prednisone. However, Elan researchers and officials insisted that this was never a viable option. One official said, "Pre-treating patients was never considered inside the company. It is very hard to give steroids to older AD patients, and steroids have side effects." Another official explained that the anti-inflammatory effect of the steroid was likely to inactivate the vaccine.

Two Wyeth researchers presented their research on AN-1792, and both are convinced that the vaccine is efficacious and that the new vaccine, ACC-001, should have comparable efficacy with less toxicity. One researcher said there are three hypotheses for the encephalitis associated with AN-1792:

a. **Direct toxicity.** He insisted this was a remote possibility.
b. **Reactivation of a latent neurotrophic virus.** There is no reproducible evidence of this.

c. **An unusually high level, altered quality, or aberrant target of the humoral or cellular responses.** He believes this is the most likely.

Poster 1: A study of peripheral blood samples (collected post-trial) from ~150 patients in AN-1792 Study 102 and Study 201. The researcher explained that the T-cells were prepped and looked at with the ELISPOT method, "There were a few inflammatory T-cells in Study 102, but more in Study 201 [the one in which patients died]…The difference in the two studies was the addition of a little detergent (PS-80) in Study 201, which was necessary for the formulation, and it seems that the detergent produced the inflammatory T-cells…The detergent loosens aggregation, which stimulates inflammatory T-cells…We now have a good idea why AN-1792 causes encephalitis, so we are engineering out the molecules that cause it. The conjugate vaccine engineers out the C-terminus."

The poster conclusion was: "No clear differences in T-cell reactivation were noted between patients who developed encephalitis and those who did not. Many patients in Study 201 exhibited Th1 responses without clinically evident encephalitis. Therefore, it must be perceived that other predisposing factors play a role."

Poster 2: A study that may have found a way to determine responders in advance by looking at the levels of gene expression of a panel of best predictors for encephalitis and IgG. The panel is not commercially viable at this point because it requires tests for about 18 encephalitis predictors and 15 IgG predictors. However, the researcher said this test will be done in the clinic with patients getting the immunoconjugate ACC-001.

2. ACC-001, an immunoconjugate (a revised vaccine), which is in preclinical development. Wyeth and Elan are collaborating on this. There was no new data at this meeting on this agent.

3. Beta secretase and gamma secretase. These are "in discovery" in the lab but have not yet progressed to preclinical animal studies.

4. AAB-001, a monoclonal antibody that is in Phase I development. An expert said, "The antibody should be safe. The question will be efficacy because it is not as potent (as the vaccine)."

LILLY'S LY-450139 (gamma secretase inhibitor)

There has been a concern that inhibiting gamma secretase – an enzyme which generates beta amyloid in the brain – could interfere with other essential physiological processes and cause unacceptable side-effects. However, early data indicates this gamma secretase is safe.

A PK study of QD dosing in beagles found:

- A dose-dependent decrease in CSF Aβ.
- An increase in plasma Aβ levels was associated with threshold plasma compound levels.
- The Aβ decrease in CSF was more persistent than in plasma.
- After six months of repeat dosing, Aβ levels in both CSF and the hippocampus were equivalent to controls at all doses, indicating that after washout, Aβ production normalizes to control value.
- Chronic elevation of plasma Aβ does not result in significant accumulation of Aβ in either CSF or the brain.

A 14-day Phase I study of LY-450139 compared various oral QD doses (5 mg, 20 mg, 40 mg, and 50 mg) to placebo in 37 volunteers over the age of 45 without Alzheimer's. No significant side effects related to the drug were found. Blood levels of beta amyloid were reduced following drug administration each day, with greater reduction seen after higher doses. LY-450139 was detected in CSF, but there was no change in the concentration of beta amyloid in CSF in this study.

A Phase II study of 70 AD patients treated for six weeks. There was no statistically significant difference in Aβ in the CSF. A Lilly official said, "We feel that we are actually on the right track, and we are starting to see the kind of change we want to see in the CSF…We want to do some small (Phase II) dose optimization studies before we go into Phase III studies."

Phase I Study of LY-450139

Measurement	Placebo	5 mg LY-450139	20 mg LY-450139	40 mg LY-450139	50 mg LY-450139
Pain	4	2	1	3	4
Ecchymosis	4	3	2	1	3
Rash	2	0	1	1	4
Myalgia	1	1	0	4	1
Back pain	3	1	1	1	0
Constipation	0	0	1	1	2
C_{max}	N/A	23.9%	27.7%	52.4%	19.2%
Median T_{max}	N/A	1.00	1.00	1.00	1.00
AUC (ng•hr/mL)	N/A	241	1220	1400	3300
$T_{1/2}$	N/A	2.42	2.60	2.36	2.63
Change in plasma $Aβ_{total}$ as a % of baseline after first dose	7.5%	90.4%	81.6%	62.5%	59.9%
Change in plasma $Aβ_{total}$ as a % of baseline after 14^{th} dose	8.7%	95.3%	84.9%	74.3%	71.7%

Asked why Lilly would go forward with this gamma secretase after another pharmaceutical company reported toxicity with its gamma secretase inhibitor, a Lilly official said, "We may have run into a little good luck with this…There is little to suggest that you really have to inhibit notch fairly completely to run into the toxicity (the other company encountered) in animals…We found LY-450139 has a fairly short half-life – about 2.5 hours – which a lot of times is a bad thing, but in this case may work to our advantage in that notch inhibition only occurs for a fairly brief time during the day…so you are incompletely inhibiting notch cleavage, which may be fairly well tolerated or may not have downstream consequences… We did safety studies before going into the clinic, and we didn't see anything to preclude us from going to the clinic. And tolerability in the clinic has been excellent…We set up the trials to look very carefully for toxicity associated with notch inhibition, and we've not seen any evidence of that."

Pfizer also has a gamma secretase in development, and a Pfizer researcher said this Lilly data is "comforting to see."

MERCK'S beta secretase inhibitor

Merck researchers reported on their use of the X-ray structure of beta-secretase to improve the potential ability of their test compounds to inhibit beta secretase. A researcher said, "Previous animal studies that used genetic engineering methods to eliminate the beta secretase indicate that this enzyme can be blocked without significant health effects. We hope the same will be true of beta secretase-inhibiting drugs in humans." Merck researchers announced that they have developed a sensitive assay to monitor beta secretase (BACE-1).

MYRIAD GENETICS' Flurizan (r-flubiprofen, MPC-7869)

A researcher from the University of California, San Diego, presented the results of a 21-day, randomized, placebo-controlled, safety and tolerability Phase I study of daily administration of Flurizan (400 mg, 800 mg, and 1600 mg) in 48 healthy elderly volunteers. He reported no serious adverse events, no dropouts due to adverse events, and no statistically significant difference from placebo in adverse events. Flurizan is an NSAID with no Cox inhibition that is believed to reduce beta amyloid-42.

A one-year Phase II trial in about 200 mild-to-moderate Alzheimer's patients is ongoing in the U.K. and Canada. It is expected to be completed in 1Q05.

NEUROCHEM'S Alzhemed (NC758)

Sources were disappointed with the lack of any substantial additional data on Alzhemed at this meeting. The only new data was the addition of a few more patients out to 21 months in the open-label extension study, and these showed that the drug appears to have an effect, but the degree of effect did not appear impressive, and the numbers were small. In addition, the best data – stabilization of cognitive function – was greater in mild AD than in mild-to-moderate AD.

Alzhemed interferes with the ability of beta amyloid proteins to "stick" to each other, form plaques, and accumulate in the brain. As a researcher put it, "It inhibits to a great extent fibril formation."

Earlier this year, researchers reported on results of a randomized, double-blind, three-month, Phase II trial in 58 people with mild-to-moderate Alzheimer's, comparing Alzhemed to placebo.

- Six patients (two on drug and four on placebo) dropped out during the double-blind part of the study. Three of them withdrew due to side effects (nausea/vomiting in two patients; weakness/weight loss in one patient).
- An investigator said there were no serious side effects related to Alzhemed, "Nausea and vomiting were the most common side effects, and they tended to occur very early, mild, and self-limiting…Typically, they disappeared and did not recur during treatment."
- Alzhemed was detected in the cerebrospinal fluid (CSF) at the two higher doses (100 mg and 150 mg), suggesting that it successfully crosses the blood brain barrier (BBB). Levels of beta amyloid protein circulating in the CSF were reduced after three months of treatment in the highest dose groups. A researcher also said there is a dose-dependent decrease in $A\beta_{42}$ CSF levels, with a mean decline of 25% with three months of treatment.

At the end of 12 weeks in that trial, all participants were allowed to continue on drug in an open-label extension study for an additional 21 months; that study is still ongoing. All 19 of the patients completing 20 months were still above baseline on ADAS-cog at that time point.

A 950-patient, 18-month, randomized, double-blind, placebo-controlled, Phase III trial is ongoing in North America. This trial is comparing Alzhemed 100 mg BID, Alzhemed 150 mg BID, and placebo – all over standard therapy. The dose will be titrated in this study, though this wasn't done in the Phase II trial. The primary endpoint is ADAS-cog and CDR-SB at 18 months, and a key secondary endpoint is structural MRI

Phase II Alzhemed Results

Measurement	Placebo n=13	Alzhemed 150 mg BID n=14	Alzhemed 100 mg BID n=16	Alzhemed 50 mg BID n=15
Mean age	72.5	74.2	76.6	74.3
Primary endpoint: ADAS-cog at 3 months	0.7	1.5	0.3	1.6
Open-label extension (n=42)				
Completed 16 months	---	26 patients	--	---
Completed 20 months	---	19 patients	---	---

(brain atrophy). An official said, "It is well known that you have atrophy with progression…If we can show a reduction in progression of atrophy, that is sufficient to get a disease modification claim…The study is powered to show a 20% reduction in brain atrophy, and for approval we want to show a 2.5 point difference in ADAS-cog with a p-value of 0.05 and powered 90%…If we do a study with a compound that is a different approach and show a change in progression, and we are first in class, it would allow approval based on one study, but we are not waiting for that – because if we have the ADAS-cog data but not the MRI data, then we would need a second study, so that is why we are starting additional studies."

PRANA'S Clioquinol

Sources were skeptical about this zinc and copper metal-protein-attenuating compound (MPAC), more commonly referred to as a chelator, but the data so far looks promising. The theory is that inhibiting zinc and copper ions from binding to Aβ helps to dissolve the Aβ and prevent it from accumulating. A researcher said, "Chelation, Alzhemed, and the immunoconjugate (vaccine) are all equally effective in animal models. The issue will be toxicity and efficacy in humans, which mice don't reliably predict…There was some toxicity with chelation in Japan." Another expert said, "I'm dubious. It is a wacky idea. There is no reason to put cold water on this, but I'm a 'show me' person."

Other agents in development include:

- **Ratnasanpil**, a compound of 70 traditional Chinese Tibetan medicines (herbs). A study from China showed it improved open-field behavior, possibly prevented neurodegeneration, and lowered Aβ in the serum of transgenic mice.

- **ANGIOTECH'S Paxceed.** This is a formulation of micella paclitaxel. A poster reported no inflammatory reaction as with cremaphor forms of paclitaxel. It is soluble in saliva and binds in the bloodstream to serum albumin for bioavailability. In a mouse study, low and medium doses – but not a high dose – improved fast axonal transport in the spiral ventral root. Researchers concluded this "may be a candidate for future studies in AD and other neurodegenerative disorders with tauopathies."

- **AVANIR PHARMACEUTICALS' AVP-923.** This oral BID combination of dextramethorphan and quinidine sulfate has finished its second Phase III trial, and the company expects to submit it to the FDA in late 2004. It is intended to be given on top of standard of care for pseudobulbar affect (emotion lability), but it may help with other symptoms.

- **EBEWE PHARMACEUTICALS' Cerebrolysin**. A study from the University of California at San Diego reported that this reduced amyloid deposits around blood vessels in transgenic mice.

- **JSW RESEARCH'S JSW-2.** This private Austrian CRO is working on a vaccine for AD. It is just starting toxicity studies and may be ready for an IND in about a year. Currently, a large study is ongoing in transgenic mice, looking at different doses and duration of treatment. An earlier version of this agent, JSW-3, produced aggression in mice at two months, but a company official thought that was due to over-dosing, so the dose has been reduced for JSW-2.

- **LILLY** has a monoclonal antibody in preclinical development.

- **PANACEA'S PAN-811.** This is being investigated as a neuroprotectant.

- **SERVIER'S S-18986.** This is a potentiator of AMPA-type glutamate receptors. A preclinical study found no neurotoxicity to rat brains after chronic, high dose treatment and apparent neuroprotective effects. This drug is currently in Phase I trials.

- **WYETH'S SRA-333.** This 5HT1a-antagonist is thought to have pro-cognitive properties. It has a half-life of six to eight hours. A PK study showed it is safe at doses of 2 mg, 5 mg, and 10 mg. It is in Phase II development to treat the cognitive deficits of AD with BID dosing.

BEHAVIORAL DISTURBANCES IN AD

In patients with dementia, behavior disturbances, including psychosis, agitation, and aggression, occur in ≤90% of patients. There is no pharmacologic intervention approved by the FDA to manage aggression related to dementia. Atypical antipsychotics are commonly used off-label to treat these symptoms of AD, especially in nursing home patients. One source estimated that there are as many AD patients on atypical antipsychotics as schizophrenic patients, but data at this meeting suggests the benefit may not be as great as thought – and there may be differences in how well the various atypicals work.

An increased risk of stroke and metabolic syndrome with atypical antipsychotics is a concern for many doctors, but it doesn't appear to be putting a chill on use so much as service as a caution, though some doctors are beginning to believe that atypicals are less alike in AD than in schizophrenia. Several sources suggested that Bristol-Myers Squibb's Abilify (aripiprazole) and AstraZeneca's Seroquel (quetiapine) may have advantages over Johnson & Johnson's Risperdal (risperidone) or Lilly's Zyprexa (olanzapine) in AD. A doctor said, "I don't think there is a dramatic difference in the products, but that is still being sorted out."

A meta-analysis by Indiana University researchers looked at 11 randomized, placebo-controlled trials of the pharmacologic treatment of aggression in dementia. They concluded: "Although atypical neuroleptics might lead to a statistically significant effect size in treating aggression related to dementia, the clinical relevance of their effect is minimal. We found no data to support the use of either anticonvulsants or SSRIs."

Researchers at the University of Southern California presented a meta-analysis of 19 published and unpublished studies of atypical antipsychotics in Alzheimer's patients. The data suggested that:

- "For every 6-13 nursing home patients with dementia who benefit over 12 weeks with risperidone (Johnson & Johnson's Risperdal), there will be one cardiovascular adverse event and one death."
- "Databases for other atypical antipsychotics are too small and the efficacy results less clearly reported to make similar assessments, but the CVAE and death risks are of a similar order of magnitude and the efficacy is not likely to be greater."

Antipsychotics in AD Aggression

Drug	Effect	Higher risk (drug vs. placebo)	p-value
Cardiovascular Adverse Events			
Bristol-Myers Squibb's Abilify (aripiprazole)	.48	Placebo	.54
Lilly's Zyprexa (olanzapine)	3.04	Drug	.12
AstraZeneca's Seroquel (quetiapine)	.15	Placebo	.05
Johnson & Johnson's Risperdal (risperidone)	2.28	Drug	.02
All	1.14	Equivalent	.83
Deaths			
Abilify	2.12	Drug	.09
Haloperidol	1.99	Drug	.12
Zyprexa	2.42	Drug	.02
Risperdal	1.66	Drug	.06
Seroquel	1.01	Equivalent	.99
Tiapride	1.01	Equivalent	.99
All	1.83	Drug	.00

FOREST LABORATORIES' Namenda (memantine)

Every neurologist questioned is prescribing Namenda for at least some patients, and all predicted that usage would continue to increase. Namenda has performed in clinical practice pretty much as doctors expected. In general, Namenda is used primarily for outpatients, not nursing home patients, though there are nursing home patients who can benefit from it. However, it is not clear whether Namenda can reduce the negative behavior effects of AD patients.

Among the physician comments about Namenda were:

- *Rhode Island:* "My expectations weren't high, but it gives people more hope…A lot of patients request its use early (off-label)."
- *Pennsylvania:* "It has met my expectations, but they weren't high. It has a little efficacy, but it is not dramatic…Use will go up because doctors are still getting educated about it, and there are still new patients asking for it. It is possible some patients are coming off it because of no effect – you can tell in about three months if there is an effect – but there are no patients going on it…The new data that Namenda in combination with Aricept may bump use, but I wouldn't change practice based on that."
- *South Carolina:* "I think doctors are still experimenting with it; there is still a physician learning curve. The pent-up demand is over, so the growth has flattened, and now it will grow more slowly. There is no dramatic improvement, but everyone has some positive patient stories."

Speakers presented conflicting information on the ability of memantine to affect negative behavior in Alzheimer's patients.

1. **Pro:** A review of a randomized, double-blind, placebo-controlled, monotherapy trial of 20 mg/day memantine in 252 outpatients not taking any antipsychotic medications.
   - Agitation, as a side effect, occurred less frequently with memantine than placebo (18% vs. 32%, $p<.05$).
   - In an intent-to-treat analysis with last observation carried forward, the neuropsychiatric inventory (NPI) score with memantine was statistically significant at Week 12 but not at Week 28. The pre-specific analysis found changes in NPI-domain scores favored memantine in nine of 12 domains.
     - Emergence of symptoms post-baseline: Only agitation/aggression was statistically significant in favor of memantine over placebo.
     - Improvement of symptoms at endpoint: Only agitation/aggression was statistically significant in favor of memantine over placebo.

2. **Pro:** A review of a 404-patient trial of 20 mg/day memantine in combination with Aricept (with atypical antipsychotics permitted).
   - Agitation, as a side effect, occurred less frequently with memantine than placebo (9% vs. 12%).
   - The NPI score was statistically significantly better with memantine at Weeks 12 and 24. By domain, memantine reached statistically significant superiority in agitation/aggression, irritability/lability, and appetite/eating.

3. **Con:** Agitation was greater with memantine than placebo in a 403-patient, randomized, double-blind, placebo-controlled, U.S. Phase III trial of memantine monotherapy in mild-to-moderate AD. There was a statistically significant improvement in the one primary endpoint of ADAS-cog vs. placebo, starting at Week 8 and continuing at all further time points out to Week 24. In the second primary endpoint – CIBIC – the memantine group did better at every time point starting at Week 4.

Measurement	Placebo n=202	Memantine n=201	p-value
Completers	83%	82%	---
Withdrawals for adverse events	5.0%	9.5%	---
Withdrawals for insufficient treatment response	2.5%	0	---
Agitation	5.9%	7.5%	---
Somnolence	1.0%	7.0%	---

FOREST LABORATORIES' Nermexane

There was no new information at the meeting on this follow-on to Namenda, but a Forest official said it is currently in Phase IIa development. Data may be available at the American College of Neuropsychopharmacology (ACNP) meeting (December 12-16, 2004, in San Juan, Puerto Rico) – if it is analyzed in time – or otherwise in 2005.

MISCELLANEOUS

Among other interesting findings at this meeting was a poster from India that suggested a new concept:

- Protein mis-folding is the bottom line molecular error in all amyloid-related diseases (e.g., AD, PD).
- The protofibril-intermediates in the amyloid aggregation pathway could be the main culprits.
- Tiny, doughnut-shaped protofibril structures are more likely to attack the cell membranes and cause destruction to surrounding cells than plaques are.
- To date, drug design and development have focused on breaking up amyloid deposits...but…future new studies should be directed at…inhibiting the early stage of protofibril formation.

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