## Europe-U.S. Regulators Mull Prevention Trial in Familial AD

*In memory of Malcolm (Butch) Noonan, Part 4 of this series.*

16 November 2010. The setting looked more like a United Nations venue than your typical meeting room or conference center—speakers arranged in an inner circle, each seat equipped with individual monitors and global power adapters, proceedings monitored discreetly from behind darkened glass in the back. But international politics was not on the agenda on 8 November 2010 at the European Medicines Agency's (EMA) sparkling modern offices in London's Canary Wharf business district. Instead, U.S. and European scientists, pharma researchers, and patient representatives spent a day with EMA regulators; officials from the agency's transatlantic counterpart, the Food and Drug Administration, joined by video link at 6:45 a.m. Washington time, though some had been listening since 4:00 in the morning. The charge of the day was to begin a dialogue toward the shared goal of offering therapeutic treatment and prevention trials to families with autosomal-dominant Alzheimer's (for extensive background on this form of AD, see Alzforum's Early-Onset Familial AD section). These families are excluded from participating in such trials, even though they have contributed immeasurably to the progress of Alzheimer's disease research over the past two decades and may harbor unique scientific potential for finding better drugs for all Alzheimer's disease.

A treatment trial designed specially for this population would be unprecedented. "The really new topic here at the EMA today is treatment of the pre-symptomatic state. This is a prospect that has never been touched in the regulatory framework. It is a very new discussion, and today is a starting point," said **Cristina Sampaio**. Besides being a clinical pharmacologist at the University of Lisbon, Sampaio serves on EMA's Scientific Advice Working Party, which was established by the Committee for Medicinal Products for Human Use. Sampaio co-chaired the meeting together with **Bruno Flamion** and **Kerstin Westermark** of the EMA. **Russell Katz**, who directs the FDA's Division of Neurology Products, led the FDA delegation.

This gathering was timely. It came not only on the day Eli Lilly and Company announced its purchase of Avid, a biotech company known for an amyloid imaging agent that is expected to receive FDA approval soon and to enable earlier-stage trials in Alzheimer's disease, but also the day before the New York Times featured an article by its reporter Pam Belluck on the promise of such trials in familial AD in a special "What's Next" Science Times section featuring "hot" fields in science. (For more information on the projects mentioned in the Times article, see ARF API series, ARF DIAN series, ARF ADNI update, and ARF ADNI series).

The EMA had organized the meeting in response to outreach by scientists of the Dominantly Inherited Alzheimer Network (DIAN). This collaboration of U.S.-British-Australian scientists to date has enrolled 125 of a planned 400 members of several dozen families with autosomal-dominant AD into a comprehensive six-year biomarker study of preclinical AD. From the get-go, DIAN scientists had intended to offer their study participants a treatment trial, and the London meeting represents the latest step in their effort. A prior meeting with industry representatives held on 23 March 2010 in Geneva, Switzerland, had made clear that the biopharma industry would consider making their drugs available for this novel kind of trial, but wanted to

hear from regulatory agencies whether the regulators would support such trials and what kinds of trial design they would want to see. In Geneva that same week, DIAN scientists led by **Randall Bateman** of Washington University, St. Louis, Missouri, and EMA's Sampaio, began planning a first such discussion. Initially expected to be small, the gathering grew when several dozen industry scientists requested a seat in the room. **Maria Isaac** of the EMA, who led the planning, told ARF that this level of industry interest is unusual, and had prompted the agency to host a larger event than originally envisioned.

Moreover, Huntington's disease was added to the agenda because this neurogenetic degenerative condition poses similar challenges to autosomal-dominant AD. Having launched large observational studies as well as a systematic preclinical drug development effort, the HD field may soon be poised for similar kinds of trials in what Huntington's researchers call "pre-manifest" disease. All told, some 70 people rushed through London's pouring rain on a cold Monday morning, surrendered their dripping umbrellas at the door for instant wrapping in the agency's smart "umbrella manager" machines, and settled in for a long day of discussion.

The upshot? Both the EMA and the FDA expressed great interest in such trials and took the same view on most of the big questions. Regulators rarely tip their hand in these exploratory conversations. Their guarded language can invite parsing and divining—a bit like the famously cryptic statements by the former chairman of the Federal Reserve, Alan Greenspan. Teasing aside, the FDA's **Russell Katz** actually offered crisp guidance on one key question on which trialists need clarity, that is, which outcome measures the FDA would consider appropriate for a trial in pre-symptomatic participants. Because these people function normally, traditional clinical tools of showing whether the drug did the patient any good are useless. Katz said that a biomarker that has a lot of congruent evidence, even if it is not yet formally qualified as a surrogate, combined with a measure of subtle cognitive deficits, might be acceptable for such trials in ADAD. It would be preferable to have previously shown, in trials of the treatment in patients with sporadic AD, that there was a good correlation between the biomarker and a more traditional measure of cognitive function. However, even without that, the FDA would consider for review a trial that showed improvement in a relevant biomarker and in a sensitive measure of cognitive functioning in patients with inherited AD who did not have symptoms, according to Katz. Researchers took notice. "Biomarker plus a cognitive outcome—that, to me, was the clearest progress of the day," said **Stephen Salloway** of Brown University Butler Hospital in Providence, Rhode Island, a DIAN investigator and member of its clinical trial committee.

In another positive note for families urgently waiting for new drugs, the regulators said that, given the limited number of study participants available for ADAD, one successful trial might suffice for approval. Typically, regulatory authorities require two such trials. But on a separate hope DIAN investigators are nursing—that the regulatory agencies would invoke an existing pathway called Accelerated Approval—Katz said the agency was not ready because it still had too few data to judge how strongly these biomarkers predict a future clinical benefit. However, to scientists parsing the oracle, the door on this option seemed ajar. "If the data from observational studies and drug studies using biomarkers continue to converge, we think this may yet become an option," noted Bateman. DIAN scientists would prefer this pathway,

because it gets drugs to patients faster. It enables a drug to receive the agency's conditional blessing based on positive biomarker results, and allows the sponsor to demonstrate that the drug is clinically useful during subsequent Phase 4 observation. If those data come, the drug receives a full stamp of approval; if they do not, the agency withdraws approval.

Scientists asked regulators whether ADAD could be designated an orphan disease, as is HD. This disease category affords financial advantages to drug developers, and ADAD is rare enough to qualify. However, discussion with the EMA and FDA made clear that in order to receive this status, a drug would have to be presented as being specific to the orphan condition, and what the DIAN investigators really want is to develop drugs in ADAD as a steppingstone toward preventing all AD—late-onset and sporadic. Salloway said that, to DIAN investigators, orphan designation makes less sense than an alternative option Katz laid out, namely that of developing and approving a drug for ADAD as a specific subset of all AD. **Baltazar Gomez Mancilla** from Novartis Biomedical Research Institute agreed, saying: "Orphan indication is a secondary aspect." (For more on these issues, see Part 3 of this series.)

A sticky issue in designing preclinical trials is how to handle placebo controls, and it proved contentious at the EMA meeting, as well. Some volunteers resent undergoing a study's procedures without the hoped-for benefits of a drug. In both ADAD and HD, some say they would consider learning their genetic status if they could join a trial, but not if they end up on placebo. The Alzheimer's scientists in London unanimously said their trials would use placebo controls to ensure scientific rigor, and offer drug to all participants after the blinded phase is over. To these scientists, the burning questions at this stage lie more in the specifics of whether they can design a trial that does not require participants to learn their genetic status, yet that does not accidentally reveal people's status to them by dint of a drug's known side effects. Detailed design questions such as these are where the DIAN scientists will focus their efforts next.

In contrast, the Huntington's scientists were split between some who favored placebo controls and others who vehemently opposed their use. "Patients will never go for it; physicians will never go for it," said **Sir Michael Rawlins**, who chairs England's National Institute of Health & Clinical Excellence (NICE). Rawlins recommended the use of historical controls, whose past success he cited for the development of such drugs as penicillin, sulfonamides, and others. Likewise, **Nancy Wexler**, Columbia University, New York, who co-discovered the mutation that causes HD and has promoted research and awareness for the disease throughout her career, cautioned that patients might not comply with randomization. Both EMA and FDA representatives insisted on placebo, however. Without this built-in control, they said, trials would become uninterpretable and unable to support regulatory approval. "If you do a study, then it has to be one that is interpretable. If you do a study that you consider ethical but is not interpretable, that is not acceptable," said Katz. Other HD scientists agreed with this stance.

Debate grew heated for a while but, in the end, generated a mutual understanding whereby a trial might forgo placebo controls for a drug that already had proven effective in manifest HD. In this scenario, trials in pre-manifest could conceivably proceed against historical controls. This is a more classical situation, and quite different from the new paradigm that had drawn the audience that day: that of testing

unapproved candidate drugs in preclinical disease, Sampaio said. She noted that trials against historical controls only work when the drug's effect size is large, and cautioned that neither HD nor AD research have to date produced a drug with a large effect size in clinically established disease. For the new paradigm of testing a drug preclinically that has not proven effective in clinical disease, placebo controls will be indispensible, the scientists and regulators finally agreed.

This discussion highlighted a difference between the HD and AD research fields. While the former operates from an assumption that drugs will help along the continuum of disease from preclinical to overt, AD researchers increasingly interpret a string of negative trials in mild to moderate AD to mean that drugs may well help at the preclinical stage but not once disease is apparent. "In AD, there is a concern that drugs given later do not work. There is a concern that promising therapies are failing in trials because they were too little too late. The disease appears to have a self-propagating, self-fueling, autocatalytic process, with inflammation and functional disconnection," said **Nick Fox** of University College London. At least for anti-amyloid drugs, the best chance may lie in dousing the flames early. "It is increasingly clear that there is a very long pre-symptomatic period. What has moved us forward in our effort for trials now is the recognition from biomarker and imaging studies that we can see this period, characterize it, and stage it. It is our window of opportunity," Fox said.—Gabrielle Strobel.

## What, No Argument? Speakers Agree on Trials for Familial AD

17 November 2010. Part 1 of this series highlighted the main points of discussion at an 8 November 2010 meeting held at the European Medicines Agency (EMA) in London. Called "Expert meeting in familial neurodegenerative disorders. Developing medicinal products for pre-symptomatic carriers: Autosomal dominant Alzheimer's disease and Huntington's disease as models," the meeting drew regulators, scientists from academia and pharma, as well as patient representatives. Part 2 of Alzforum's coverage continues with what scientists from inside and outside DIAN, and from both sides of the Atlantic, said about the prospect of such trials.

**Nick Fox**, a DIAN investigator at the University College London, made a case to the regulators that ample biomarker research on the years preceding symptoms, combined with a disheartening string of drug trial failures in AD, meant that future drug treatment research had the most to gain by focusing on the pre-symptomatic stage. "We must treat earlier," Fox said.

Fox pointed out that a five-year delay in age at onset would cut in half the projected prevalence by the year 2050 of 13 million AD cases in the U.S. alone. To get there, science first needs a study population that will develop AD with certainty and can be found. Furthermore, scientists want to test and understand anti-amyloid drugs initially in people who have this pathology but are otherwise healthy, not in older people with the complicated mixture of different pathologies and co-morbidities that currently enroll in conventional mild to moderate AD drug trials. A trial in ADAD carriers would bridge mouse and human treatment data, Fox said. To design a good trial, Fox said, scientists want to separate people by how far away they are from age of onset, because a person who is within a year of that dreaded age has more advanced AD

pathophysiology, but can also tolerate more risk of side effects than a young adult who still has 15 years to go. All this argues for ADAD.

"We should not call this 'prevention,' by the way," Fox added. "We would prevent only the clinical manifestation in people who already have the molecular process of the disease unfolding in their brain." Given that the mutations are nearly fully penetrant, the pathology is clear, and imaging, biochemical markers, and cognitive decline all predate symptoms, scientists can stage how close to onset a person is. Changes in some biomarkers appear many years before symptoms; however, the immediate, one to two years prior to symptoms are marked by converging imaging, biochemical, and subtle cognitive changes.

"We can identify people who will be clinically manifest in a few years and show that the disease is happening in them," Fox said.

Because this population is so small and already under much strain, Fox urged companies and scientists to design the best possible trial collectively, and regulators to be creative in trial design such that ethical and moral objectives can be heard. For example, relatives with symptomatic AD should be allowed into the trials if they wish. Fox, who has cared for and studied ADAD families for so long he now treats affected patients who used to come along to play at their parent's appointments decades ago, readily acknowledged that his involvement with these families informs his thinking as much as the underlying science.

The families are taking days off work and traveling far to participate in DIAN. It is a demanding study that puts participants through a two- to four-day wringer of testing that runs the gamut of AD biomarker and neuropsychology research. Still, a 23-year-old woman and her 30-year-old brother who last month underwent their first such visit in Boston told this reporter that participating in DIAN was an empowering way of dealing with their family's ordeal.

**Randall Bateman** of Washington University, St. Louis, Missouri, updated the audience on the latest DIAN data. As of 13 October, 106 people had completed their first visit. Nearly all complied with the clinical assessments, four out of five with imaging, and two-thirds with the requested lumbar puncture. Twenty people are within plus or minus three years from their expected age at onset; a majority is younger. The non-carriers show no cognitive deficit on the MMSE or the CDR sum of boxes assessments, whereas carriers who are five, even as far back as 10 years, younger than their expected age at onset do show subtle decrements. On structural MRI, DIAN replicates Fox's and Rossor's findings that the rate of atrophy accelerates before age at onset, although those curves separated only by a little. PIB-PET showed a wider separation in uptake in the precuneus and caudate brain areas.

Importantly, CSF measurements in these volunteers show that carriers overproduce Aβ42 relative to Aβ40. Mutation carriers produce more Aβ42 than do non-carriers. "We believe this reflects the pathogenic mechanism. Carriers produce more Aβ42. As the disease progresses, their CSF levels drop, but 20 years prior, carriers start out higher than non-carriers. We think this is of great interest," Bateman said. Overall, the pathobiology emerging from this cohort is similar to that of late-onset or sporadic AD, and can be detected 15 years before symptoms. "This group appears well suited for

proof-of-concept studies, and eventually secondary prevention studies," Bateman concluded.

At the EMA, three European experts who are not involved in DIAN endorsed the premise of treating pre-symptomatic carriers of AD mutations. First, **Bruno Dubois** of Paris's Hospital de la Salpêtrière, France, placed DIAN's study population in the broader context of a shift in terminology that is spreading through the field as clinicians grapple with how to define pre-dementia stages for research and clinical trial purposes. Last July, a set of expert panels largely from the U.S. had proposed revised diagnostic guidelines (see ARF related news story). In October, a different (though partly overlapping) group of clinical leaders from Europe and the U.S. published their own attempt at clarifying exactly what to call the stages preceding overt AD (Dubois et al., 2010).

As per this new lexicon, people who have deficits in episodic memory tests such as word recall, and who also have abnormal biomarkers, would be told they have "prodromal AD." This is a symptomatic stage that reaches back three to five years into the pre-dementia phase. People at earlier stages—that is, those long five to 15 years prior during which they have no clinical expression of the underlying disease—would fall into two groups. Asymptomatic people who have biomarker changes should be told they are "at risk for AD," not that they have "preclinical AD." Using the latter term would consign people to fear even while scientists do not yet know for certain how these biomarkers predict future clinical disease. "This is very important," said Dubois. In contrast, people with autosomal-dominant mutations and biomarker changes do have "pre-symptomatic AD," Dubois said. The population for which DIAN proposes therapeutic trials falls into this latter category. To date, 83 percent of carriers in DIAN have mutations in presenilin-1, 3 percent in presenilin-2, and the rest in APP.

Second, **Caroline Graff** from the Karolinska Institute in Stockholm, Sweden, emphasized the appeal of clinical trials for families with these dire genetics. At her center, researchers know about 50 at-risk relatives. Recent data on some of them confirm biomarker findings from other studies that CSF Aβ42 drops significantly in carriers at least nine years prior to their expected age of onset. Graff disputed a statement that sometimes crops up in these discussions, namely that autosomal-dominant AD is different from sporadic AD, or even that each mutation generates its own disease. In her experience working with AD patients, "with ADAD the signs and symptoms are the same as sporadic AD, except the onset is usually younger and it progresses faster," Graff said. Some clinical variability occurs in all neurodegenerative diseases even within a family; it is not especially pronounced in ADAD, other AD clinician-researchers agreed.

Graff cited the example of a family that came to her center in 2005 with a suspicion of HD but turned out to have a presenilin mutation that brings on disease in a person's thirties. "We now have contact with eight individuals of this family who are at 50 percent risk, seven of them in the age range for clinical trials," Graff said. DIAN scientists are exploring how either the entire observational biomarker protocol, or a clinical trials portion of it, can be expanded to include participation from European families at Graff's and other centers in Sweden and other countries, said Bateman.

Third, **Harald Hampel** of the University of Frankfurt, Germany, endorsed the initiative of biomarker-driven drug trials for mutation carriers. In a review of existing data on CSF biomarkers in FAD mutation carriers, he noted that it is highly concordant (e.g., Almkvist et al., 2003; Moonis et al., 2005; Scheuner et al., 1996). Like DIAN and Graff's data now, these older papers showed an Aβ42 decrease in CSF a decade before symptoms and an increase in tau some five years prior to symptoms. Likewise, imaging research has produced a signature for prodromal AD, Hampel said (Reiman et al., 2010). Regional cerebral glucose metabolism by FDG-PET, fibrillar amyloid deposition by PET, and regional gray matter atrophy by MRI all yield strongly concordant results that together identify prodromal AD. Research by Fox and **Martin Rossor** at University College London has over the years shown that global and regional atrophy accelerates some five to three years prior to symptoms, with annual rates of change that apply consistently, Hampel noted (Ridha et al., 2006). As in sporadic AD, in ADAD metabolic abnormalities precede shrinkage by some years (Mosconi et al., 2006).

Hampel said that organized, comprehensive studies such as DIAN were the logical next step to follow on single-center studies, and he applauded DIAN for adopting ADNI protocols so data can be directly compared. DIAN's preliminary biomarker and imaging data conform closely not only to prior, smaller ADAD studies but also to the preclinical staging graphs that grew out of ADNI. "That opens a considerable window. The biochemical and imaging data suggest abnormal APP metabolism, and axonal/synaptic/neuron losses are evident in a pre-symptomatic phase years before clinical onset. This is useful in clinical trials," Hampel said.

Hampel showed a staging slide from a recent review that overlaps closely with those that many researchers are showing at conferences these days (Hampel et al., 2010; also see Perrin et al., 2009 and ARF Webinar with Cliff Jack). On a time axis, the commonly accepted staging scheme starts the disease process out with amyloid deposition/CSF Aβ42 lowering around 15 years prior to symptoms, followed by FDG-PET reduction, then by MRI atrophy, then CSF tau increase five years prior, cognitive performance some three years prior, and then a functional decline around the time of conventional diagnosis.

**General Consensus: Check. Now for Specifics**

So far, all agreed. How, then, can scientists actually conduct preclinical trials? **Paul Aisen** of the University of California, San Diego, and the Alzheimer's Disease Cooperative Study, put an example design on the table for the regulators and pharma scientists to discuss.

To Aisen's mind, the optimal time of intervention may be an early stage of amyloid deposition. A trial of an anti-amyloid drug could be designed for a broad population across ADAD families and enroll participants whose brains have brain amyloid. Such a trial would necessarily have to use a biomarker outcome, because people at this stage remain years away from clinical symptoms. This outcome could again be amyloid imaging or CSF, or it could be MRI. MRI makes sense to Aisen, because the normal subjects in the ADNI cohort show marked atrophy if they also have brain amyloid. The same is true for FDG-PET and even the crude MMSE test: The decline in these markers among the normal ADNI group is disproportionately due to those people who are amyloid positive, Aisen said.

But do these biomarkers respond to drugs? Little is known. Amyloid imaging did decrease with drug, and increase with placebo in one study (Rinne et al., 2010).

Specifically, Aisen proposed this design for regulatory discussion: a randomized, parallel group study with a select anti-amyloid treatment given for two years, followed by an open-label extension to ensure every person gets access to treatment. Biomarkers would constitute primary outcome measures, including MRI, FDG-PET, amyloid PET, CSF, cognition, and patient-reported outcomes. Clinical outcomes would follow post-study. "We can power such a study in ADAD with group sizes ranging from 25 to 250," Aisen said. Dubois added to this that the results of French observational studies suggest follow-up clinical outcomes should choose tasks that flag highly AD-specific deficits, such as free recall and cued recall tests stressing hippocampal function. In Part 3 of this series, read how regulators from Europe and the U.S. chewed on this proposed trial design.—Gabrielle Strobel.

## What Regulators Say About Trials in Familial AD

18 November 2010. How did the regulators parry these new proposals and questions? Eight EMA officials and nine FDA officials took part in the discussion about preclinical trials in autosomal-dominant AD at an 8 November 2010 meeting held in London at Europe's government drug agency. Read these excerpts and divine for yourself how they think about risk and benefit at this point. The excerpts are notes from this first of several conversations, not binding statements. EMA and FDA statements appear by agency, not by its individual representative.

**Question:** Can ADAD drugs receive orphan drug status?

**FDA:** AD itself by far exceeds the maximum prevalence of 200,000; ADAD stays well below it, so it is possible in principle. To obtain orphan drug designation, you'd have to make the case that ADAD is a subset of AD that needs different treatments. Or you'd have to make the case that ADAD is different from AD in general.

**EMA:** We take the same view. Since we consider the condition together with the drug, the drug would have to be developed specifically for the subset and could not be developed for the broad condition. That would exclude the use in the broad condition.

**Question:** what about existing and exploratory products that are not specific to ADAD?

**FDA:** To get an orphan indication, you'd have to make the case that the product is specific to that genetic form, i.e., to fewer than 200,000 patients.

**Question:** What impact would designating ADAD as orphan have on trial design?

**FDA:** The rules for qualifying a drug are the same for an orphan or non-orphan condition. You have to have safety and efficacy data. In theory, there is no difference between orphan or not orphan, though in practice, we do impose slightly different standards. If the condition is very rare, we may not require two independent studies. In this particular setting, we may require a single study.

**EMA:** We look more to the strength of the evidence, less to whether you have two trials.

**FDA:** So do we. We can apply the one-study standard plus totality of evidence, which can be supplied from other studies.

**FDA:** We can't say in advance what outcomes would support approval. A very robust outcome, a clinical outcome, and a biomarker outcome would be appropriate in a setting like this.

The other clinical issue that might be raised when we talk about study design is this question of great interest to you: approval based on a surrogate only, without a concomitant clinical outcome. We have a rule and part of a law that allows us to approve on the basis of an unvalidated surrogate. ADAD might be a place where that could be considered. We do not think at the moment that would be appropriate, but it is a potential approach for study design.

**EMA:** On the possibility of getting orphan disease designation, either the drug is specified for ADAD or, if the drug is applicable for both ADAD and LOAD, it is unlikely that orphan designation will come forward. We are looking at a product that can be developed for both conditions—you spoke of doing ADAD trials as proof of concept because there has been so much difficulty in sporadic AD trials. ADAD trials would be an opportunity not only to give the patients from these families a chance to participate and have a treatment, but also to create new trials as proof of concept for LOAD. So the orphan pathway seems difficult.

If the drug is not specific to ADAD, in the first instance it might be studied in ADAD as proof of concept. But it also might come as full development of ADAD and then later also go for sporadic AD. So we have to discuss if you have the tools for development in familial AD. For that we can accept development with just one clinical trial. We can see a situation of doing just a single trial in ADAD in part because you showed us stable information for biomarkers in FAD. On the other hand, there are a few troubling data coming from sporadic AD that might make trial design extremely difficult. [Editor's note: This refers to increased, then decreased, atrophy in responders to AN1792 immunotherapy.] My question here is how similar or different ADAD and sporadic AD are in this regard.

**FDA:** We are certainly open to approving a drug just for inherited AD. That is an option. Whether that disease is ultimately different from sporadic is something we can discuss. The genetics describe a discrete subset that would be appropriate for development and approval independent of whether the drug then works in sporadic AD, too. That is feasible from a regulatory standpoint.

**EMA:** We agree. ADAD and sporadic AD are the same clinically; we see no reason to separate them. We view ADAD as a cluster of AD. We want it to be no longer neglected in trials.

**Question:** How about placebo controls?

**FDA:** Placebo is appropriate in this setting and should be used. That is caught up in the question, How long can you keep people on placebo in this setting? The trial must be long enough.

**EMA:** Let's discuss the alternative of high-dose versus low-dose drug. That can give the same result as placebo control, but is more acceptable to patients.

**FDA:** We would accept that. We would accept any trial that is designed to show a treatment difference clearly. High dose/low dose is more acceptable to patients, but it is a bit deceptive because the stated goal is to show a difference. This has ethical implications of its own. It becomes a semantic exercise where you need to show a clear difference and then use an effective and a likely non-effective dose, so it's a slippery argument.

The bigger issue is that historical controls were suggested in the presentations, and we insist that concurrent control is appropriate.

**EMA:** We need to be pragmatic in these discussions. In this field, everything has failed in the last 10 years. We are having nasty surprises with trials that have shown deleterious effects. We cannot assume when putting a drug in a trial that it is going to be effective, or that there will be no problem. To do a trial in a small population, the only patients that exist in the world, will be a unique opportunity. We cannot play around with designs that have confounding factors, so we cannot get around placebo.

A number of good markers show when the familial patients are likely to develop dementia. These markers are very reliable from a variety of data. If the patients really want to partner in this adventure, they have to accept these rules. It is extremely difficult to succeed here, so we cannot introduce additional confounds. Low dose/high dose in essence is a partial randomization. We cannot afford that.

**Rawlins:** Huntington's is a different situation. Currently, a significant cohort of historical controls is being collected. In HD, the mechanism of neurodegeneration in pre-manifest and manifest is the same. And drugs work on both. For pre-manifest HD, placebo-controlled trials are a non-starter.

**FDA:** That is in the context of where there is an effective drug for manifest disease. That is a pre-manifest study you do not need to do. If a drug exists and works in manifest, and pre-manifest is just a milder stage, then you do not need to study it. You want to avoid doing a study in a particular population because you can do it, but that study does not lend itself to interpretation. That would be a bad outcome.

**Rawlins:** For ADAD, how about a futility trial to check that your treatment is ineffective and move on to the next?

**FDA:** There is no regulatory objection to that.

**Rawlins:** ...and compare treatment with historical control.

**FDA:** That is problematic. It depends on the effect size. If you have a drug that stops disease in its tracks, and you can clearly see that in a reasonable period of time, then yes, but we do not expect that from AD drugs.

**EMA:** Agreed.

**William Thies**, U.S. Alzheimer's Association: For ADAD, there would be no difficulty recruiting to a placebo-controlled trial. If you confuse the results in this group, it will confound to an extent we cannot accept.

**Nick Fox**, University College, London: We have an FAD support group. Their message is a very clear willingness to take part in a placebo-controlled study. There are no disease-modifying treatments for AD at the moment that they would forgo by taking placebo. Their willingness may change when an effective drug shows up. [For more on this support group, see Part 4 of this series.]

Low dose in lieu of placebo is a sleight of hand. It may only be useful to protect people from finding out their status through side effects. A real issue we have to deal with is how we let people participate who do not want to know their status and might find out through the side effects.

**Question:** Can we define endpoints in ADAD trials?

**EMA:** Despite small sample size, the DIAN biomarker data are robust in characterizing this population. The MRI data recap what Fox has produced, and the CSF data are in line with what we know from CSF biomarkers in sporadic AD. These data support the bulk of biomarker knowledge we have, and this knowledge is very good. We can predict relatively well for an individual in a family when he or she is going to develop symptoms. That is extremely useful to design a trial.

Where I think things become complex is in the definition of tools to define the endpoint, because the data for amyloid imaging and MRI atrophy rates for this population are as complex as they are for sporadic AD. They have the same type of problems as endpoints, as showing drug response as they have for the sporadic disease. For instance, we know atrophy can go up and down in sporadic AD and are unsure what is good and what is bad. We know amyloid imaging can change, but we do not know if this is good or bad. So it is probably better to rely on a cognition measurement. Which one? It would have to be sensitive enough. So far, data from ADNI suggest the CDR sum of boxes as the most sensitive outcome. Would we be able with small sample size to have a result with that? That is a question.

**FDA:** For sporadic AD, we require an effect not only on a cognitive measure, but also on a global measure. In ADAD pre-manifest disease, we would want a clinical outcome. But we are open in conjunction with an effect on a surrogate or even multiple surrogate markers, to use a cognitive outcome on the subtle early change instead of the clinical.

You can make the argument that in this setting, a change in subtle cognitive testing even before patients complain of impairment together with biomarker would be adequate.

**Paul Aisen**, University of California, San Diego, ADNI, DIAN: This is a very interesting discussion. To clarify, in the ADNI database, we find the CDR sum of boxes to be the most efficient measure of decline only in the prodromal pre-dementia, what many in the U.S. might call the MCI phase. As far as ADAD is concerned, we are hoping to move earlier than this prodromal phase. DIAN is interested in moving our clinical trials into the preclinical or asymptomatic stage. In that stage, the CDR sum of boxes shows no change with time. It is not useful as an outcome measure.

But we have seen in PAQUID and ADNI that it is possible to see subtle cognitive change in this asymptomatic population. As the FDA has suggested, it may be very feasible to link our efficacy biomarker to a subtle cognitive change as a way of demonstrating a sign of clinical manifestation.

We do not have a means to show a global clinical measure. By definition, you can't do that in an asymptomatic population. But with the biomarker and the subtle cognitive change, we have a way to move forward.

**Bruno Dubois**, Hospital de la Salpêtrière: I completely agree. The CDR sum of boxes represents clear functional decline. We need to move earlier. My only point of discussion with Paul is that I view these patients with the early cognitive change as symptomatic. I take that as the first symptom.

**Aisen:** You have been very helpful in clarifying the lexicon. The field needs help there. I am not talking here about the complaints that would bring the patients in to see the clinician. The subtle cognitive change I mean is before that. But yes, it is a symptom.

**EMA:** We are discussing several issues at the same time. One is doing trials in asymptomatic genetic families. That is totally new. Another is doing trials in patients that are pre-MCI/eMCI/at-risk patients, which is also new.

These are two populations. Is it wise to mix them in the same trial? If you do, at least stratify. Can the endpoint be the same for them both? Even in terms of safety, the risk/benefit may be different for these two populations.

The number of patients is small and you want maximal sample size, but putting the two populations together carries risks. If you move forward, come to scientific advice with EMA's CHMP and discuss the protocol. These issues go beyond the scope of the forum here today. We are eager to discuss details.

**FDA:** Our comments pertain to the ADAD population, not the sporadic population. Whether they would apply to the latter is a larger question that would require considerable thought. To clarify: Accepting biomarker and an early cognitive change would be acceptable at this point for ADAD.

**EMA:** But even within the families, you have two different populations. People in the pre-dementia stage and people years earlier than that are in different stages of evolution.

**Question:** What is your feeling about the current state of the biomarker data?

**EMA:** We have worked hard in the last year to try to validate the biomarkers. We are looking closely at specificity and sensitivity.

**FDA:** There is good evidence that they track disease closely; some are more sensitive than others. They are useful for choosing folks for trials. The only position we have taken is that they are not ready for use as sole outcome measures. We are not saying which one is best. We think as many as possible should be incorporated in trials so we can learn how they move in response to treatment. We have no favorite at this point.

**Question:** In closing, can the regulators say they would make a decision based on biomarker and cognition?

**EMA:** Yes.

**FDA:** Yes, this is an outcome package we would consider.

## Families Talk About Treatment Trials

19 November 2010. At the end of a meeting held 8 November 2010 at the European Medicines Agency in London, **Bruno Flamion** of the EMA capped the day's discussions by saying: "What has changed today? We learned convincingly that autosomal-dominant patients have been excluded, and now realize they could be an extremely valuable population for trials."

But what did the audience hear from those families themselves? No AD family representatives were there in person that day, but several people spoke and showed videos on their behalf. **Nick Fox** of University College, London, said, "The families are incredibly generous and motivated to take part in trials. We asked three of them what they would say if they were here." Read these excerpts:

**Woman 1**, in her thirties: "My great-grandmother had the disease, my grandfather did, my mother did. I have the gene and my brother has it. I will get the disease. I have to live with that every day."

**Woman 2**, in her fifties: "My father started having problems in his mid-fifties. He was making mistakes at work, needed prompting, and was diagnosed with AD. Soon after, one of his younger sisters, and a brother, also, started developing the same symptoms. I remember that my grandfather had had similar problems; my grandmother had looked after him. I put two and two together. I realized something must be going on here."

**Man**, in his forties: "Dad developed symptoms at 60. We noticed that an aunt and uncle had it, too, and found out that his father had died in a mental hospital of similar symptoms. I made a family tree. I found lots of names and sent that to Martin Rossor and John Hardy. Within a couple of years, they came back to us and told us they discovered the fault on chromosome 21."

**Woman 1:** "I chose to have the test done. I wanted to know whether I had it. I was hoping not to, but something inside me just knew I had it. The genetic counseling was

fantastic. They made me think about how my whole family would think about it, not just I."

**Woman 2:** "I chose not to have the test. If I want to do something, I do it now. I don't defer it to later."

**Man:** "Our support group is a fantastic forum. Most important to me, it helped me understand there are other families that have been through the very same thing. We felt very isolated. We asked: why us, why only us? Through the support group we now understand there are others who have been through a very similar journey."

**Woman 1:** "I was planning to get married but kept putting it off. When I had the test results, we said let's go and do it, which is exactly what we did!"

**Man:** "We live very much in the day. We don't save for the rainy day so much."

**Woman 1:** "I would not take back the test for anything."

**Woman 2:** "I am the age when it starts. Whenever I lose something or forget something, I wonder, is that it? My husband looks at me and I know exactly what he is thinking. I tell him: 'Don't look at me like that!'"

**Man:** "Whenever I forget something, I wonder, is it now starting? In our family we joke about it but it is a real worry."

**Woman 1:** "Being part of the research, you can only help. I want to pave the way for the future of my family."

**Man:** "I don't have to have taken the test to participate in the trial. I just want to participate to help in the cause; the benefit to me is secondary."

**Woman 2:** "I hope there will be a lot more medications that at least will slow it down so people can enjoy the quality of life they have longer. And be treated like people, not just be stuck in a wheelchair for the rest of their lives."

From the other side of the Atlantic, **William Thies** of the Alzheimer's Association said that people with familial Alzheimer's disease have a greater commitment to the next generation than do people with sporadic disease. "They are acutely aware of what they are passing on to their children. That makes them very willing to take part in research and accept risk." About the current situation, the most frequent remarks he hears is, "Why can't we get our parent into clinical trials? It is not fair." Thies urged industry and regulators to do away with this exclusion. "We owe the families a better outcome. They are a unique population, and useful for trial design for prevention trials in sporadic AD."

Huntington's disease families had a representative at the EMA meeting in **Astri Arnesen**, who leads the Norwegian Huntington Patients Association. Arnesen spoke about her mother, who had Huntington's for 30 years, and her four siblings. "My oldest brother and I are healthy. I chose to find out my status because one of my daughters really needed to know. I did not inherit the disease gene. My sister's status

is uncertain. I thought she was positive, but she also has Asperger's syndrome and now I am thinking she may not have HD. My other sister has HD, and my younger brother Arne Dag was diagnosed at age 35."

About this brother, Arnesen said: "When did he get sick? It is hard to say. He was an excellent student and studied engineering. But he never quite finished. He worked as a taxi driver and a guard. Ten years prior to his diagnosis, he was severely depressed.

"Like in familial AD, many HD patients are parents and have economic responsibilities when the disease hits them hard. Even a small delay in progression would make a huge difference for us. The HD community has had little hope, and like in AD, there is tremendous anxiety in these families. Huntington's is very difficult to live with."

Arnesen showed a video of Arne Dag, now 40, who said into the camera, in fluent English: "I would like to test a medicine as soon as possible. It would give me more hope. I hope science is on my side, that there is a possibility for me to test some medicine. Other people think the same way."

So where do things stand? The ball is partly in industry's court, but pharma representatives said little in the way of specifics at this particular meeting. **Baltazar Gomez Mancilla** of Novartis Biomedical Research Institute addressed the audience, saying that his company is interested but sees considerable uncertainty about practical and ethical issues, such as when to treat, how to randomize, and what effect sizes to expect. Gomez Mancilla noted that he was encouraged by the FDA and EMA's joint support of biomarkers and a cognitive outcome as acceptable endpoints, and noted that longitudinal studies that further define the similarities and differences between ADAD and sporadic AD—such as DIAN and ADNI—would help his company move forward. DIAN is this fall collecting nomination packets from pharma companies for their respective compounds (see ARF related Honolulu story). In London, Bateman said some have already been submitted, and additional pharma companies have indicated they intend to submit.

When these trials finally happen, it will be not a day too soon for families. It is easy to forget that the families whose research participation enabled the discovery—to much fanfare—of APP and the presenilin genes in the 1990s continue losing loved ones now just as then. The disease is still eating its way through their younger generation. Before the London meeting, on 4 November 2010, Malcolm (Butch) Noonan passed away from Alzheimer's disease in Falmouth, Massachusetts, at the age of 55. He appeared briefly in the 2004 PBS documentary "The Forgetting: A Portrait of Alzheimer's," which publicized familial AD in the U.S. Two of his older sisters had died earlier, both in their fifties; one, Fran, was shown receiving a visit by her siblings in the film when she was unable to speak any longer. In a videocast 2004 lecture about ADAD, Malcolm spoke as the second of five siblings about how isolating it was for him, the sixth of 10 children, to grow up with the "unknown monster," without a mother who was dying from Alzheimer's, with an overwhelmed father, and a house full of children who were each struggling in their own way. Malcolm also spoke about his search for research opportunities as a young adult. At the time of this video lecture, he had been recently diagnosed. Butch continued to participate in research and donated his brain to science. As did his two affected sisters Maureen and

Fran, Butch left behind adult children. They are now facing 50-50 odds of being next, while having young children of their own.—Gabrielle Strobel.