DIAN Grows, Gets Ready for Therapeutic Trials

On 14 April 2012, the Dominantly Inherited Alzheimer Network (DIAN) Pharma Consortium met in Washington, D.C., to exchange the latest information on DIAN's preparation for therapeutic trials. On the road toward doing something unprecedented—offering preventive drug trials to carriers of Alzheimer's disease mutations who live scattered around the world—the day marked progress on growing the network, nailing down outcome measures, first glimpses at longitudinal data, and regulatory clarifications. Here is a summary in two parts.

As of April 2012, DIAN had enrolled 242 participants, **John Morris** of Washington University, St. Louis, Missouri, told the audience of some 50 scientists in academia and industry. With that, the network met its original recruiting goal of 240. One hundred thirty-three of 212 (63 percent) are confirmed mutation carriers, of whom 75 are asymptomatic. In the past, there had been doubt that participants would comply with DIAN's extensive requirements, or would stay with the six-year study. In fact, most participants complete all assessments; even the lumbar puncture rate exceeds 80 percent, and nearly all return for their repeat visits. "This is a highly dedicated group," Morris said.

DIAN needs more participants to be able to create the statistical power of the therapeutic trials it plans to offer. Currently, DIAN is continuing to enroll toward a revised goal of 400. DIAN's Therapeutic Trials Unit (TTU), led by **Randall Bateman** of Washington University, is surveying 75 additional clinical locations in the U.S., Europe, and Canada. The DIAN TTU asks the sites how many ADAD family members are in their care. It also inquires about facilities and resources, and other criteria to probe the site's potential to join future DIAN treatment studies. This ongoing process to date has identified more than 300 additional asymptomatic individuals who may be interested in therapeutic trials once they learn about them and the trials are ready to recruit. Bateman expects that many more carriers remain to be discovered. "Studies usually focus on symptomatic individuals, not on their asymptomatic family members, but they are there," Bateman said.

Of the more than 320 newly identified symptomatic carriers and over 330 asymptomatic carriers, about 285 asymptomatic carriers live in Denmark, Finland, France, Germany, Italy, Japan, The Netherlands, Spain, and the U.K. Intriguingly, investigators also found seven sites in Russia and Bulgaria that are in contact with ADAD families, many of them with confirmed mutation and symptomatic status, Bateman said. One site alone noted a database of 50 families with early-onset AD that looked autosomal-dominant in their inheritance pattern, but lacked genetic verification. "We will follow up on these leads," Bateman said. DIAN is already expanding in other ways. This year, the network is adding the Mayo Clinic, Jacksonville, Florida, as the eighth participating U.S. site, as well as two sites in Germany, Morris noted.

To engage physicians and individuals from around the world, the network has launched an online portal called the DIAN Expanded Registry (see ARF related news story). Officially announced in April of this year, the portal has brought in some 65 registrants

so far, Bateman said. He stressed that the DIAN Expanded Registry is targeting specifically the small autosomal-dominant slice of the AD population, not all people interested in prevention trials for AD. For Alzheimer's prevention trial participation more generally, the Alzheimer's Prevention Initiative is launching a larger registry. For people who have a diagnosis, the Alzheimer's Association's TrialMatch service is available online or over the phone (1-800-747-2979). These three registries target slightly different populations, and their representatives pledged to coordinate among each other by referring interested individuals who came through a respective group's door to the registry that best matches their situation.

Wanted: The Best Test

At the same time that investigators reach out to find participants, they are also working internally to define the outcome measures that are most likely to pick up the subtle changes expected to occur in the years prior to dementia. A drug's potential success at preventing a person's transition from asymptomatic to symptomatic will require the cognitive measures to be significantly more sensitive than those used in trials of mild to moderate AD. The DIAN Pharma Consortium asked a working group to pressure-test whether cognitive tests in DIAN are up to the task. This work is ongoing, and longitudinal data are not available yet, but in D.C., **Martha Storandt** from WashU briefed the group on cross-sectional data gathered up to March 2012. These suggest that most of the 22 cognitive tests DIAN participants take indeed detect differences between asymptomatic and symptomatic mutation carriers. Likewise, presymptomatic carriers had lower scores on most tests than did non-carriers. On certain tests, older carriers performed worse than young carriers, whereas both young and older non-carriers performed well. On rare tests, all participants performed worse if they were old than if they were young, but carriers of all ages had lower scores than did non-carriers. One advantage of testing and detecting differences in this younger population is that age had a lesser effect on cognitive performance.

Jessica Langbaum of the Alzheimer's Prevention Initiative at Banner Alzheimer's Institute in Phoenix, Arizona, briefed the group on the API's parallel effort to pin down a handful of tests that change the most over time during the presymptomatic period, yet vary the least from person to person (for details, see ARF related news story). The winning combination of tests was similar for a sporadic and for an autosomal-dominant cohort; both included recall of word lists and paragraphs. Interestingly, the top five were slightly different if the task was to detect decline in the 10 years prior to AD diagnosis than if it was to detect decline four years prior, Langbaum said. Working with **Suzanne Hendrix** at Pentara Corporation, the scientists have in recent weeks further tested these composites by comparing them against either individual tests or a large battery, or by switching out certain tests. Each time, the original handful yielded the most power. "We have used different analytical approaches to ensure these results are robust," Hendrix said.

Reisa Sperling at Brigham and Women's Hospital in Boston, and colleagues have taken a similar approach in other datasets as part of their work preparing for the Anti-Amyloid Treatment in Asymptomatic AD (A4) trial to be run by the Alzheimer's Disease

Cooperative Study. This is a third initiative to get secondary prevention trials off the ground. These scientists, too, are finding word list and paragraph recall tests to be particularly powerful, Sperling told the assembled group in Washington. The scientists at this meeting intensely discussed this question, as numerous groups are currently trying to validate composite test batteries for those coming trials. The leaders of the DIAN, API, and A4 prevention trial initiatives have agreed to seek consensus on what the best composite might be, and to use at least overlapping measures in their respective trials such that results can be compared directly or even be analyzed together.

New DIAN Data

At this meeting, **Bateman** for the first time presented a glimpse of what kind of longitudinal data scientists can expect soon. By March 2012, some 40 DIAN participants have had two of each type of assessment (clinical, neuropsychological, MRI, FDG, PIB, CSF), and seven participants had three. By the end of this year, the number of baseline visits is projected to stand at 308; 100 people will have come for two visits, 60 people for three visits, and 10 will have completed their fourth. As the longitudinal data are coming in, they are being analyzed to estimate power for the planned trials.

Tammy Benzinger of WashU offered the latest cut of cross-sectional and some longitudinal PIB-PET imaging. Asymptomatic carriers show the first signs of amyloid deposition around 18 years prior to expected age at onset. From there, deposition spreads and becomes AD-like, even before the clinical dementia rating budges from 0 to 0.5. That spread appears to happen at roughly the same rate in each affected brain region, Benzinger said. Longitudinal data are beginning to show that, for each brain region, baseline and follow-up PIB measures correlate, such that uptake increases on the second compared to the first scan, Bateman added. How many participants a trial would need for PIB to detect a treatment effect depends on whether the treatment reduces the rate of amyloid growth, halts its growth, or even reduces the absolute amount of brain amyloid, as has been reported for two different immunotherapies (Rinne et al., 2010; Ostrowitzki et al., 2011). Thirty people per arm would be highly powered to see at least the last effect, Bateman said.

Furthermore, Bateman noted that the amyloid loads measured in DIAN, as well as other parameters such as standard deviation and annual increase in deposition, are comparable to those published for other MCI or AD observational cohorts such as ADNI and the Australian Imaging, Biomarkers & Lifestyle Flagship Study of Ageing (AIBL).

These data raise the question of which amyloid PET tracers to choose for AD prevention trials. To help the clinical and pharma scientists address it, **Victor Villemagne** of Melbourne University, Australia, compared published data on the three most developed of the available candidates, florbetapir/Amyvid, flutemetamol, and florbetaben. All three stick to white matter longer than PIB, their signal is weaker, and their dynamic range smaller. Among these three 18F compounds, there are small differences as well. Therefore, these three 18F tracers are unlikely to pick up the very beginnings of amyloid deposition as sensitively as does PIB, said Villemagne. However, each of them is well capable of detecting whether there is significant amyloid in a prospective study

participant's brain, Villemagne added. Each can predict progression and support subject selection for trials. The tracer's response to drug remains unproven, though florbetapir is being used in some ongoing AD therapeutic trials.

Florbetapir gained FDA approval for clinical use and is supported by Eli Lilly and Company; hence, it is likely to be available in the long run for trials that will last multiple years. Florbetaben was sold to the Indian company Piramal Imaging; Phase 3 autopsy data were presented at the American Academy of Neurology Conference in April of 2012 in New Orleans, Louisiana. GE Healthcare's flutemetamol just completed an autopsy study and a biopsy study (see ARF related news story). A fourth compound, 18F-AZD4694, appears promising in early studies, with a signal much like PIB's, but has not reached Phase 3 yet.

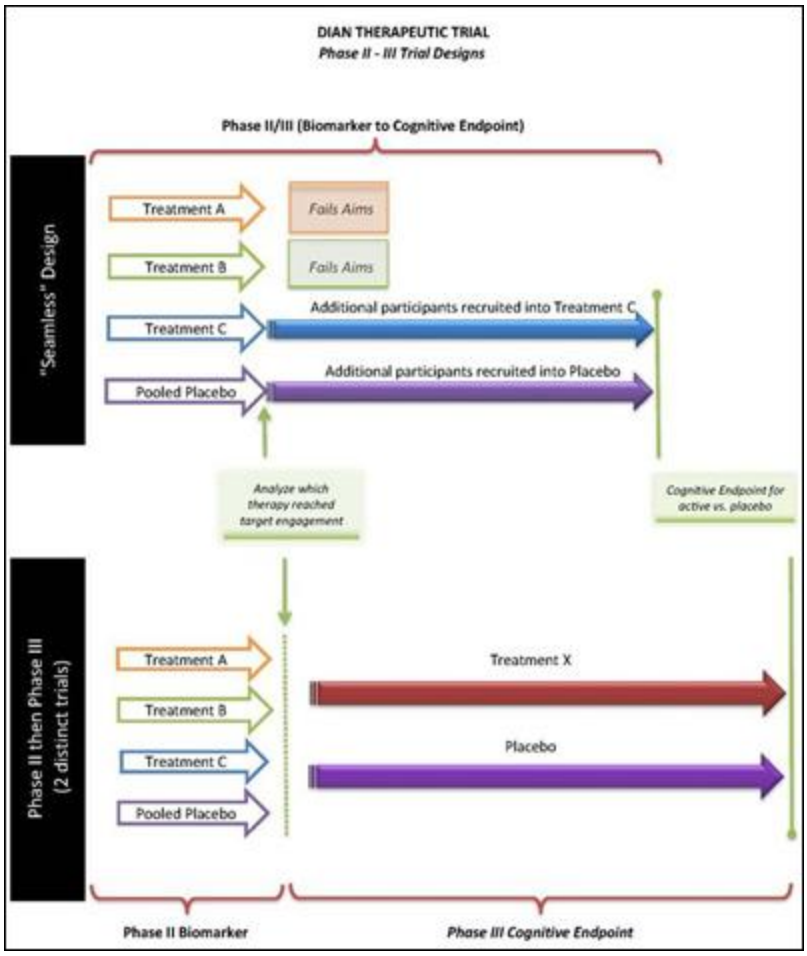
Villemagne works with Chris Rowe in a nuclear medicine center that tests all experimental amyloid tracers it can obtain. Asked essentially which tracer was the fairest of them all, Villemagne's dodge injected a moment of levity into otherwise serious proceedings, "That I leave up to you. We practice promiscuity."

Bateman presented **Anne Fagan's** latest fluid biomarker data, which, like PET imaging, are beginning to include longitudinal results as DIAN participants undergo their second lumbar punctures. As expected, plasma Aβ40 is the same in non-carriers as in both asymptomatic and symptomatic carriers. Plasma Aβ42 is higher in carriers, but the data overlap and no clear age effect jumps out. Plasma Aβ42 does not differ strongly whether carriers are 30 years or five years away from their expected age at onset, Bateman said. Fagan and Bateman also showed data comparing DIAN's CSF data to published data in sporadic cohorts using ADNI cutoffs. This comparison is limited because ADNI cutoffs were established with the help of an autopsy series and cognitive assessments, whereas the DIAN data come from living and, in large part, cognitively normal subjects, and were measured in different labs. With these provisos, the general trend in both sporadic and familial AD is that the amount of CSF Aβ42 in symptomatic individuals is reduced to about half that in controls, whereas tau and phospho-tau rise two- to threefold. "The take-home message is that DIAN CSF data are similar to sporadic AD CSF data," Bateman said.

What Sayeth the Regulator? Q&A With Rusty Katz

When the Dominantly Inherited Alzheimer Network (DIAN) convened its Pharma Consortium on 14 April 2012 in Washington, D.C, its scientists intended to brief the Food and Drug Administration on how far DIAN's work has advanced to date. Their other goal was to obtain feedback from the FDA on the study designs DIAN trialists have proposed. To this end, DIAN Pharma Consortium (PC) members asked the advice of Russell Katz, who directs the agency's neurology products division. A paraphrased and abbreviated Q&A of the conversation follows.

DIAN PC: Are there regulatory concerns in our choice of a so-called seamless design, where a biomarker phase runs into a longer Phase 3 trial, which then uses cognitive outcome measures?



Seamless trial design proposed by DIAN Therapeutic Trials Unit. View larger image. *Image credit: DIAN Therapeutic Trials Unit*

Russell Katz: I see no particular regulatory challenges to a seamless design. You need to address blinding questions and assure us that a type 1 error is not inflated in the envisioned design. It's best to lay that out prospectively. That has been done before. One more point: Let's assume arm A gets dropped and arm C continues; presumably, then, participants in arm A will be moved to C. That is not a problem.

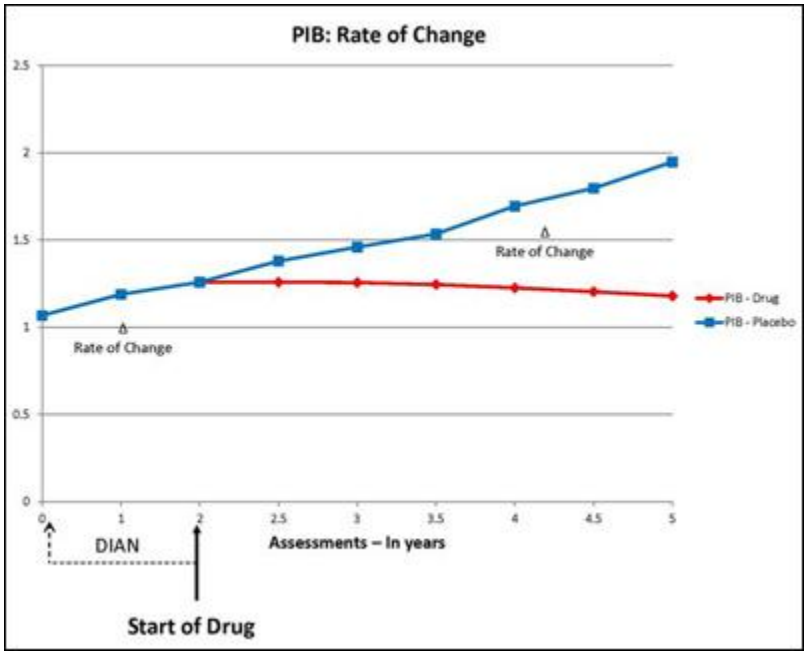
DIAN PC: Is the intra-individual rate of change an acceptable endpoint if the parent DIAN study data are used as the run-in baseline data for the biomarker and cognitive endpoint trials?

Russell Katz: Conceptually, the agency has no objections to using intra-individual change. How exactly you are planning to analyze it will be important.

DIAN PC: For example, what if a person's 20 percent per year decline in DIAN decreased to a 0 percent per year decline during the trial?

Russell Katz: You'd have to show it is statistically significant, but that is an impressive change.

DIAN PC: Can DIAN use pre-trial data on biomarkers, CSF, imaging, clinical, and cognitive to determine a change, or individual rate of change? For example, can we use data that have been collected in DIAN as a baseline for evidence that a drug has changed PIB retention?



Hypothetical change in brain amyloid before and during treatment trial. View larger image. *Image credit: DIAN Therapeutic Trials Unit*

Russell Katz: Yes, this would be fine, assuming data collection was done post-randomization as it was done pre-randomization, i.e., during DIAN.

DIAN PC: Would the FDA concur, as indicated in November 2010 (see ARF related news story), that for individuals with autosomal-dominant AD and pre-manifest disease, a subtle clinical change in conjunction with an effect on a surrogate or even multiple surrogate markers could be acceptable for approval?

Russell Katz: Yes, we are open to that, for example, an effect on a composite cognitive measure.

DIAN PC: Would one such study be considered sufficient evidence?

Russell Katz: We are open to that, too. But the effect has to be robust, on the primary outcome, on the secondary outcomes. It has to be unassailable.

DIAN PC: If two drugs show benefit in the biomarker trial, are there any problems from a regulatory viewpoint of taking both forward (i.e., same placebo group, etc.)?

Russell Katz: I see no significant regulatory problem there.

DIAN PC: Would change in CDR-SOB as a single primary efficacy measure be suitable for registration?

Russell Katz: We are open to that. We have not signed off on that formally, but have told sponsors to flesh this out for us. We recognize that very early on, when people are asymptomatic, the usual rules are difficult to apply. DIAJN PC: Would a time-to-change outcome measure or a single cognitive measure or composite be sufficient for registration?

Russell Katz: Again, that is possible.

DIAN PC: How might these different endpoints affect the labeled indication if the trial is positive?

Russell Katz: It's hard to know exactly what the label would say. We would be reluctant to grant a disease-modifying claim just on the basis of a clinical outcome. If you have a change on a biomarker and on a clinical outcome, then we contemplate granting a disease-modifying claim. What kind of a claim a positive trial would support also depends on whether all people who carry different mutations respond in the same direction.

DIAN PC: Based on FDA feedback to date, the agency prefers one IND holder, i.e., DIAN, with multiple product INDs, rather than the alternative of having multiple IND holders using the same protocol. What are the obstacles to having multiple IND holders?

Russell Katz: It is hard to imagine that we would accept multiple IND holders for the same trial. It would be a complicated trial and an administrative nightmare to deal with multiple sponsors. The regulations say that the sponsor is responsible for the conduct of the trial. There has to be one entity. With I-SPY, for example, that is the Foundation of the National Institute of Health (FNIH). I cannot imagine more than one IND holder.

DIAN PC: Under a single IND scenario, DIAN will need to meet certain obligations. DIAN will be responsible for IND amendments, safety reports, etc. Could these obligations, particularly those related to the reporting of serious adverse events (SAEs) to the FDA, be delegated or transferred to DIAN's pharma partners?

Russell Katz: No. You can't ask folks who are not the sponsor to handle an obligation of this sort that you are proposing. Amendments, safety, etc., have to come to us through the

sponsor. Suppose there is a safety issue. It has to come to us; it has to be disseminated to all. How is that possible with multiple IND holders? I have asked about this idea internally, but we think it is not workable. I know it is of concern to some pharma partners. We are happy to sit down with the group to try to figure this out, but we are fairly clear the answer is no.

Russell Katz: What is the objection to a single IND holder?

DIAN PC member, speaking for the member's respective company, not the entire committee: It is not scientific or medical. Some companies are concerned about risk to their drug if they are not controlling the interaction with the FDA, especially if it is a drug that is under FDA review for approval based on other trials the company is also doing. For example, DIAN has not done much SAE reporting in a registration clinical trial. When an SAE comes in, sometimes it is difficult to determine if it is related to treatment, especially in such an unusual cohort.

Russell Katz: I don't understand why it can't happen under one IND holder. I have not heard anything today that would require multiple INDs, and see problems on our side coordinating separate studies with separate INDs.—Gabrielle Strobel.