

Pursuing Combination Therapy Development for Alzheimer's Disease
An FDA/Alzheimer's Disease Allies Meeting

Rockville, MD
November 29, 2012

To date most advanced pharmacologic trials for Alzheimer's disease (AD) have focused on monotherapy primarily targeting amyloid. Tau, inflammation and other pathways have not been afforded the same level of attention for their role in potentially augmenting the disease largely because AD drug development relied heavily on single-pathology models of the disease constructed around the amyloid hypothesis. However, recent scientific evidence points to the possible multifactorial etiology of Alzheimer's disease spurring thought that the optimal treatment of Alzheimer's disease may involve the use of drug combinations targeting amyloid and multiple other disease pathologies at different points in the disease course.

On May 14-15 2012 the National Institutes of Health (NIH) held a major summit on the treatment and prevention of Alzheimer's disease. Discussions about alternative pharmacologic targets and combination therapy development were included in four out of the six sessions held during the NIH 2-day summit. Research recommendations produced at the end of the summit also included multiple calls for testing Alzheimer's therapies in combination and developing more effective tools and experimental models that better simulate the disease. With the release of *The National Plan to Address Alzheimer's Disease* that same month, the scientific community, advocates, industry and government officials began coalescing around the goal of compressing the timeline for clinical trials in Alzheimer's disease.

In the wake of these exciting developments and at the urging of officials at the U.S. Food and Drug Administration, ACT-AD and the Critical Path Institute co-hosted a high level meeting in November of 2012 to lay the foundation for pursuing combination therapy development in Alzheimer's disease. This was done by exploring how combination therapy development and pre-competitive collaboration have been successful in other disease areas and industries and applying those principles to the current state of research and therapeutic development for Alzheimer's disease.

The meeting was successful in establishing that it is the right time for pursuing combination therapy development for AD. Collaboration will be essential for achieving combination development and while challenges to collaboration among industry partners are formidable, they are not insurmountable. The next step for the field is to come together through an intensive, consensus-building process for achieving the shared vision of treating and preventing AD. ACT-AD is organizing a follow-on retreat to generate a roadmap for how this shared vision can become a reality through combination therapy.

Pursuing Combination Therapy Development for Alzheimer's Disease
An FDA/Alzheimer's Disease Allies Meeting

Rockville, MD
November 29, 2012

Meeting Report

I. Introduction

With the recent disappointing results from Phase 3 trials of anti-amyloid agents for Alzheimer's disease (AD), researchers and drug developers in the field are considering additional approaches to changing the course of the disease. There is an increasing recognition that, like cancer, Alzheimer's is a complex disease that may benefit from a combination therapy approach. Combination therapy development has been successful in other life-threatening diseases in part because collaborative approaches were established to identify necessary pathways and tools that enabled more efficient trials. An important related development is the FDA's 2010 publication of draft guidance on the codevelopment of multiple drugs for use in combination, which needs to be understood in the context of AD. Thus, the ACT-AD coalition of 50 national patient-centered organizations, with co-sponsorship by the Coalition Against Major Diseases (CAMD), convened its fifth annual ACT-AD meeting devoted to the following objectives:

- To explore how partnerships could foster more robust collaboration on AD in order to encourage the development of combination therapies.
- To gain greater clarity about the FDA's requirements for the development of multiple therapies in combination for the treatment of AD and explore the feasibility of practically designing clinical trials for more than one AD therapy.

Mr. Dan Perry (ACT-AD) and Dr. Diane Stephenson (CAMD) welcomed participants and framed the day's discussion in terms of the urgency of AD as a public health crisis and the clear signal from the FDA that combating this disease is a major priority for the Agency.

The morning session featured presentations from a diverse group of speakers on the case for precompetitive collaboration and how industry cooperation in healthcare and beyond has been effective for overcoming complex and shared challenges, existing models of collaboration in other disease areas, the history and design of combination therapy trials in oncology, and the unique challenges of combination trials in AD. Participants then heard from the FDA on the relevant guidance for novel-novel drug codevelopment and engaged in an extensive discussion with Agency representatives to understand how the guidance applies AD. In the final session, a panel discussion, participants built upon ideas introduced in the preceding session to formulate a set of important concepts and recommend actionable next steps.

II. Importance of Precompetitive Collaborations

Michael Krams, M.D., Janssen Pharmaceuticals

The current state of Alzheimer's drug research and development (R&D) is a relatively siloed exploration of individual compounds. Further, in neuroscience R&D generally there is often little understanding of targets before compounds are developed. In contrast, in other fields clinical trials typically only occur after there is good understanding of the underlying basic biology in order to define the indication and the targets prior to exploring appropriate compounds. To apply

this method to AD requires abandoning the traditional unidimensional mapping from compound to indication in lieu of an integrated, cooperative, multidimensional mapping process that shares information across compounds.

Dr. Krams proposed that solving the complex problem of AD requires an engineering approach. In this paradigm, the first step is to deconstruct the problem. Then the field can work collaboratively to build a roadmap for a coordinated research effort across multiple sectors toward prevention and treatment of the disease. Dr. Krams proposed that this roadmap-building effort should occur in the context of an intensive meeting of all of the relevant stakeholders to obtain broad buy-in from the field.

In order to move toward solutions, Dr. Krams suggested a series of basic research questions to be addressed. First, the question of who should be treated remains open since it is known that amyloid deposition occurs many years prior to the diagnosis of “dementia.”¹ At a recent Alzheimer’s Association Research Roundtable meeting, one suggestion put forward for answering this question is to build upon the findings of the common pathogenic role of amyloid precursor protein in both AD and Down’s syndrome by establishing a natural history study of people with Down’s syndrome and conducting pharmacological intervention in sentinel cohorts.² The second basic question is about how to treat this disease. Dr. Krams concluded that it is now clear that AD is more than a pure amyloid pathology, and thus, like other complex problems such as HIV and cancer, its treatment will require combination therapy. He noted that the field can learn from efforts in other complex diseases that are grave public health threats where academics, regulators, and the health industry worked collaboratively from establishing targets all the way to proof-of-concept stages in a precompetitive manner.

The third question revolves around how to observe a potential treatment effect. Based on the Jack et al. model,³ Dr. Krams suggested that the field build a biomarkers-based “GPS” system to identify the position of subjects on their trajectory toward developing dementia. He proposed that this be done in the context of a large-scale natural history study, which he characterized as an enhanced Framingham-like study modeled on the Alzheimer’s Disease Neuroimaging Initiative (ADNI), to observe biomarkers within subjects over time and establish their relationship to one another. This epidemiological study could potentially morph into a pharmacological intervention trial for symptomatic, secondary prevention, or even primary prevention stages. Finally, there are unresolved questions about when to initiate treatment. Dr. Krams advocated for considering interventions across the entire spectrum of disease development rather than focusing on only one timepoint for intervention.

¹ Bateman, R.J., Xiong, C., Benzinger, T.L., Fagan, A.M., Goate, A., Fox, N.C., et al. 2012. Clinical and biomarkers changes in dominantly inherited Alzheimer’s disease. *New England Journal of Medicine*, 367:795-804.

² Ness, S., Rafii, M., Aisen, P., Krams, M., Silverman, M., & Manji, H. Down’s syndrome and Alzheimer’s disease; towards secondary prevention. 2012. *Nature Reviews Drug Discovery*, 11:655-656.

³ Jack, C.R., Knopman, D.S., Jagust, W.J., Shaw, L.M., Aisen, P.S., Weiner, M.W., et al. 2010. Hypothetical model of dynamic biomarkers of the Alzheimer’s pathological cascade. *Lancet Neurology*, 9:119.

III. Designing a Trial for Combination Therapies

Don Berry, Ph.D., Berry Consultants

Despite the relatively well developed markers in the field of oncology, success rates are low and cancer survival rates remain abysmal. In 2006, FDA CDER Director Dr. Janet Woodcock lamented the bottleneck of the traditional clinical trials process and stated that “improved utilization of adaptive and Bayesian methods” could help resolve low success rates and reduce the expense of Phase 3 clinical trials. Adaptive trials are typically smaller, result in more accurate conclusions, address a host of questions including whether combination therapy is effective, and tend to focus on better treatment for patients. Today, adaptive design is increasingly used in academic centers, and most major companies are experimenting with it.

The oncology field has accepted for some time that combination therapy is required to effectively combat cancer, but due to poor design, early trials were not informative with regard to why some combinations worked better than others. In 1993, Berry Consultants designed a factorial trial of combination therapy for the Cancer and Leukemia Group B, which led to the approval of Taxol and marked a sea change in the history of combination therapy trials.

In an adaptive factorial design for combination therapies, patients are adaptively randomized to Drug A, Drug B, Combination Drug AB, or the control condition, and aggressive interim analysis is conducted so that at any point the single drugs or the combination may be dropped from the trial for ineffectiveness. The trial can also be expanded to test additional combinations. Dr. Berry emphasized that a clear and relatively near-term primary endpoint is critical with this design, and he acknowledged that defining such an endpoint may be challenging in AD. In addition to the primary endpoint, this design can support measurable “auxiliary endpoints” related to the different biological effects of the various drug mechanisms, and synergistic drug effects can also be modeled. Finally, this trial design addresses patient-specific responses to a single drug or combination of drugs.

This design is the basis of the I-SPY multi-center clinical trial for breast cancer. The NCI, academic breast cancer investigators, and industry have partnered in I-SPY to evaluate the impact of chemotherapy before surgery on patients with locally advanced breast cancer. The trial includes serial assessments and real-time analysis of biological markers to predict 6-month pathological complete response and, ultimately, survival. In addition, the trial is designed to respond to the need for a more efficient clinical trials process by identifying who is and is not benefiting from breast cancer therapeutics in an adapted Phase 2 trial, resulting in a reduced sample size in Phase 3 and eliminating overtreatment. Historically, Phase 3 cancer trials have required 3,000 patients with a success rate of only 30 to 40%; in contrast, Phase 3 trials based on the results of I-SPY can be as small as 300 patients with a projected success rate of 85%. Now in its second iteration, the trial has tested a number of regimens, either dropping them for futility or graduating them to a focused Phase 3 trial. The ability to nest factorial designs within an adaptive trial supports combination drug testing. Each experimental arm features drugs from different companies, and the Investigational New Drug application (IND) is held by a public-private partnership, the Foundation for the NIH.

Dr. Berry concluded that the benefits of the I-SPY approach are many, including the capability to match therapies with biomarker signatures, the automatic 40% savings in trial cost that accrues from using a common control (e.g., six arms in a trial instead of six two-arm trials), faster throughput for successful therapies, and the relatively rapid graduation of successful drug/biomarker pairs to smaller and more successful Phase 3 trials based on Bayesian predictive probabilities. This model has spawned both academic and industry trials in colorectal cancer, melanoma, lymphoma, HIV, acute heart failure, and H1N1.

IV. Challenges of Combination Therapy in Preclinical AD Trials

Reisa Sperling, M.D., Harvard Medical School

Dr. Sperling posited that the basic rationale for combination therapy in AD is that because it is complex disease, effective treatment will require addressing multiple mechanisms simultaneously, ideally mechanisms of amyloid deposition and neurodegeneration as well as neuroprotection. Even if the scope of a combination approach is limited to amyloid reduction, there are some compelling reasons for considering a combination of anti-amyloid agents. One is that the recent failures of monotherapies in Phase 3 could indicate that greater amyloid reduction is required, and potential dose-limiting toxicities encountered with one drug may be avoided if drugs are used in combination. It is also possible that effective amyloid reduction will require combinations of drugs that target multiple forms of A β . However, there are several challenges to a combination therapy approach, particularly in preclinical stages of disease: (1) It is unclear how to assess the synergistic effects of combination therapies in a short timeframe in the early stages of AD; (2) there is a dissociation between markers and clinical outcomes in Phase 3 trials; (3) the clinical rate of change is slower in early disease; and (4) there are ethical concerns about exposing high-risk but clinically normal individuals to the potential harms of a combination therapy.

The evidence from biomarkers research is clear that the pathophysiologic process of AD begins decades before dementia, and Dr. Sperling argued that while combination therapies for later stages of disease should be considered, the time to intervene is much earlier, when all the biomarkers are abnormal but clinical disease has not manifested.⁴ In addition to their utility for identifying preclinical subjects for study participation, biomarkers also have potential utility for demonstrating target engagement. While the hope is that markers can be used theragnostically, it is not yet clear which markers predict clinical therapeutic response. The field is also in need of better synaptic function markers and a greater understanding of the significance of markers in the context of clinical trials.

In spite of these challenges and needs, Dr. Sperling and colleagues are planning a trial of combination therapy in early AD. The aim of the COMBAT trial is to include drugs that decrease A β production and increase clearance (e.g., a secretase inhibitor plus immunotherapy), increase clearance of multiple forms of A β , decrease A β and neurodegeneration, and do any of these functions plus offer neuroprotection. While an adaptive trial design is intriguing, it may be difficult to implement in early AD because it is unclear what short-term marker will predict clinical response in early populations given their slow rate of cognitive decline. In addition, a

⁴ Sperling, R.A., Jack, C.R., & Aisen, P. Testing the right target and right drug at the right stage. 2011. *Science Translational Medicine*, 3; 111.

factorial design for testing combinations may be difficult because AD drugs are at various stages of development have different safety and monitoring requirements, and blinding placebo groups poses an additional challenge if drugs have different routes of administration.

Dr. Sperling concluded with the following important needs in the field to realize wins in AD drug development and improve trial efficiency:

- More biomarkers (and not only in small subsets of patients) in earlier intervention trials;
- Biomarkers that more closely reflect synaptic dysfunction (e.g., to demonstrate whether the brain functions better if amyloid is removed);
- Trials with populations who are at high risk for decline but are early enough in the AD process that neuron rescue is possible;
- More sensitive cognitive measures and other markers to detect subtle changes over short timeframes in earlier AD; and
- Guidance on how to imbed safety monitoring in a 2x2 factorial trial design.

V. Discussion

Dr. Stephenson commented that markers of synaptic connectivity are promising but, like other markers, present challenges in terms of harmonization. She suggested that the field should consider how to implement these measures uniformly across studies. Dr. Sperling responded that resting-state functional MRI is embedded in the Dominantly Inherited Alzheimer Network, the A4 trial, and the Alzheimer's Prevention Initiative, and a harmonization group is in place to oversee collection of approximately 40,000 scans from these trials.

Dr. Krams stated that many billions of dollars have gone into drug development for AD and much less into understanding the disease. Thus, he argued for reversing the balance of investment to focus on methodological studies that establish how to identify and observe patients and on more robust modeling and simulation approaches. Dr. Sperling countered that natural history studies and drug development should occur in parallel because of the discordance between observations in epidemiological cohorts such as ADNI and clinical trial populations.

One participant asked whether each of the presenters is advocating for immediately testing combinations once a drug has progressed to Phase 2. Dr. Krams affirmed that he is, and Dr. Sperling added that a combination approach is particularly important when working with populations in the early stages of disease. Because of the length of time required to know which drugs are working, sequential testing of monotherapies in this population will result in an unacceptably long wait for answers. Dr. Berry cited Herceptin as an example of how combination testing led to development of this important drug. Notably, this drug fails as a monotherapy, but in combination is a veritable miracle drug for the large group of breast cancer patients with Her2-positive tumors.

Mr. Ian Kremer, Executive Director of Leaders Engaged on Alzheimer's Disease, asked whether Dr. Krams envisions that his proposed Framingham-like study would involve a multinational population and seek international funding. If so, he asked what complications would be introduced by international collaboration. Dr. Krams suggested focusing on developing a roadmap that clearly articulates the goals of the study and predicted that such a plan will be

compelling to a diverse group of funders, including international governments. Dr. Sperling commented that the A4 trial is currently exploring international co-funding for its stage 0 natural history arm.

Dr. Neil Buckholtz, Director of the NIA Division of Neuroscience, concluded that an important need for the field and the key to fielding the types of studies the presenters suggest is to identify markers that change in a reasonable period of time. This is particularly critical for an adaptive design trial. Whether in studies of single drugs or combinations, the field must gain a better understanding of how drugs move various markers in a short timeframe as well as possess the necessary measurement precision to observe those changes.

VI. Precompetitive Collaboration & Coopetition: Lessons Learned From History and Other Industries

David Dilts, Ph.D., Center for Management Research in Healthcare

Compared to other countries, drug development in the United States is generally slower, more expensive, and less productive in terms of bringing new products to market. Dr. Dilts contended that the major reason for these discouraging trends is the lack of “coopetition.” In this model, competitor companies form a precompetitive consortium so that they can cooperatively solve a shared problem. The precompetitive space is an area where an entire industry, rather than a specific company, needs assistance and encompasses standards, data, or processes that can be common across an industry and where adoption or use provides no competitive advantage.

There are a number of highly successful stories of precompetitive collaboration in other industries that have led to major gains in overcoming shared problems and improving outcomes for all companies in that industry; for example, The U.S. Semiconductor Manufacturing Technology Consortium, the World Wide Web Consortium, and the USB Implementers Forum. Further, there are many historical and current examples that suggest the diminishing returns of working in a siloed manner. For example, the interoperability gap in the pharmaceutical industry due to the lack of shared data standards has been estimated to cost the industry \$8 to 9 billion annually. Dr. Dilts acknowledged industry’s general wariness to cooperate and in response offered several value propositions: (1) Companies that cooperate outperform their competitors, (2) working collaboratively is a good return on investment given the multiplier effect of consortium dollars, and (3) consortiums provide a fast and low-risk way to fail and learn from mistakes.

Dr. Dilts concluded that the work of AD drug development is too important to continue in the current cumbersome manner. He echoed the call for a roadmap-based, systems approach to the problem that is focused on increasing throughput. Ultimately, the most critical factor in changing the existing drug development paradigm for AD is a collective will to take action.

VII. Successful Models for Precompetitive Collaboration

A. Critical Path to TB Drug Regimens

Debra Hanna, Ph.D., Critical Path Institute

Approximately one-third of the world’s population is infected with tuberculosis (TB), and the incidence of multidrug and extensively drug resistant TB is rising. The current standard of care for active, drug-sensitive TB is a combination therapy administered over 6 to 9 months.

However, these drugs were neither developed specifically for TB nor to be used in combination, and their concomitant use results in drug interactions and adverse events. Because this regimen is poorly tolerated by patients, patients are noncompliant with therapy, resulting in increased drug-resistant TB strains. Further, although many TB patients are co-infected with HIV, existing TB therapies are not compatible with HIV therapies. Despite these grave problems with the standard of care, no new TB treatments have been approved in over 40 years. (NB: Post-meeting, a new drug for TB was approved in December 2012)

In 2010, the Critical Path to TB Drug Regimens (CPTR) was established as a public-private partnership within the Critical Path Institute (C-Path) in order to address the significant and diverse challenges facing new TB drug development, including lack of scientific innovation, economic concerns, and regulatory hurdles. CPTR's mission is to accelerate the development of new, safe, and highly effective regimens for TB by enabling early testing of drug combinations. Industry members of the CPTR operate in a precompetitive consortium framework that supports open data sharing. Other members of the partnership include academic scientists, global regulatory authorities, and civil society organizations. Dr. Hanna stated that one of the keys to success for this large and diverse consortium is creative thinking around policy issues *in parallel* with scientific innovation to ensure that the policy issues do not impede drug development.

CPTR is organized into three groups: (1) The Research Resources Group comprises several working groups to address clinical trials infrastructure, streamlining global regulatory pathways, stakeholder and community engagement, and access to drugs and appropriate use; (2) the Regulatory Sciences Consortium addresses precompetitive data sharing, including data standards/integration, markers and clinical endpoints, and preclinical/clinical sciences; and (3) the Drug Development Coalition developed the legal framework for appropriate competitive data sharing and has dealt with anti-trust issues. CPTR's work is guided by the FDA's "Guidance for Industry Codevelopment of Two or More Unmarked Investigational Drugs for Use in Combination" and "Qualification Process for Drug Development Tools."

A major milestone in the history of the CPTR was the launch of approved TB data standards using the clinical data standard preferred by FDA review divisions. Standardization in the field permits data sharing, aggregation, and querying, which is critical for leveraging large datasets for decision making. When implemented at the start of a trial, data standards lower the cost of acquiring and analyzing data. Dr. Hanna emphasized that sharing data is critical for combination novel drug development because the development process relies on modeling and simulation. *In vitro* preclinical pharmacokinetic/pharmacodynamic (PK/PD) data from single agents are used to build modeling and simulation tools that aid in understanding the drugs' efficacy in combination and how they distribute *in vivo*. Standardized clinical trials data are also required to build disease progression models that effectively simulate clinical trial designs for combination therapies.

Dr. Hanna concluded that it is clear that complex diseases require a combination therapy approach, which poses several challenges. She shared the following lessons learned within CPTR about how to meet these challenges:

- Invest heavily in preclinical tools in order to select the right combination preclinically.
- Develop appropriate modeling and simulation tools that take into consideration PK/PD parameters in order to choose the right dose for single agents in combination.

- Build a framework that supports sharing data and appropriate clinical trial design and infrastructure.
- Consider methods to advance the regulatory approval process (for example, by utilizing adaptive trial design or accelerated licensing) to facilitate more expeditious review and approval of combination therapies.

B. National Center for Advancing Translational Sciences

John McKew, M.D., National Institutes of Health

The mission of the National Center for Advancing Translational Sciences (NCATS) is to catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions. NCATS aims to develop initiatives that address bottlenecks in translation, involve a high level of collaboration between the Government and private sector, and are responsive to the needs of biomedical researchers.

To that end, two major grant initiatives are now underway within NCATS. The first is a drug rescue and repurposing program, which was established to address the problem of the lengthy, complex process required for researchers to gain access to existing compounds for testing in new indications. The program is resolving that challenge by using template agreements⁵ to streamline negotiations between intramural researchers with a drug testing proposal and the pharmaceutical company that owns the molecule. Dr. McKew stated that getting the first company to sign on to the model agreements was challenging, but after the initial success other companies rushed to join the program; they now have 58 compounds contributed by 8 companies. The second program is a microsystems initiative to develop a tissue chip for drug screening. These chips, which will mimic human physiology, will be used to screen for safe, efficacious drugs by drawing upon the best ideas in engineering, biology, toxicology. The program is funded through investments by the Defense Advanced Research Projects Agency, NIH, and the. As of July 2012, the program has issues 19 awards. In addition to these grant programs, the NCATS Division of Pre-Clinical Innovation manages a set of collaborative, non-grant programs involving collaboration between intramural investigators and outside researchers to address every aspect of the drug development pipeline.

A significant success story from the drug rescue program is identification of a repurposed drug to treat refractory chronic lymphocytic leukemia (CLL), which constitutes 30% of all leukemias; virtually all patients with CLL relapse. Patient- or primary-derived CLL and normal donor B cells were obtained and screened against a set of 4,000 approved drugs at nine concentrations, which were judged based on their ability to differentially kill cancer cells and narrowed to 30 candidate drugs. Ultimately, the program selected auranofin, an old rheumatoid arthritis drug, based on its efficacy as well as the drug's data package and the perceived ease of repurposing it in a new patient population. NCATS, the Leukemia and Lymphoma Society, and Kansas University combined their respective expertise to develop this candidate drug, and in 2 years after *in vitro* activity was demonstrated in CLL cells, the first patient was dosed.

⁵ Available to the public at <http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/therapeutic-uses/agreements.html>.

VIII. Discussion

Ms. Cynthia Bens, Vice President of Public Policy at ACT-AD, commented that one of the advantages of CPTR is its productive partnership with the Gates Foundation. There is no one major donor in the AD space, and she asked Dr. Hanna to comment on how large foundations can be urged to support AD research program, thereby reducing the reliance on industry dollars. Dr. Hanna responded that where consortia have made progress in wooing large foundations is by leveraging real products (e.g., data standards, models, drug combinations) to demonstrate how the consortium process actually works to advance the field. She predicted that once there is a win, large donors will understand the importance of investment in this space. Dr. McKew added that there is a potential for significant financial gains for companies that successfully develop an AD drug; thus, he recommended focusing on ways to de-risk the collaborative development enterprise to encourage industry participation. He noted that several companies were able gain access to private equity only after their collaboration with NCATS had a demonstrated win, and this was true for drug programs with a much smaller patient population than AD. Dr. Dilts recommended that when building a consortium, it is important to make the initial “ask” to companies small; then the consortium should be prepared to show a real output to encourage additional investment.

Ms. Bens also commented that establishing data standards in AD is necessary but not particularly compelling to potential funders, and she sought input on how advocates can better articulate the need for data standards. Dr. Hanna stated that CPTR can share a number of lessons learned on how to build the case for standards. Dr. Buckholtz noted the existence of several successful data sharing initiatives that can help bolster that case; for example, industry partners in ADNI gain access to the study data in exchange for their investment and the Alzheimer’s Association GAAIN initiative is working to collect data from new investigators into a single, accessible database. Dr. Stephenson reported that CAMD has recently published AD-specific data standards with funding from the FDA and has also pooled data from the placebo arms of 22 clinical trials into a unified clinical trials database. She commented that one of the challenges to the data pooling effort is that companies are reluctant to contribute biomarkers data. Dr. Stephenson emphasized that sharing this information is critical because, as has been observed already, the biomarker learnings from ADNI differ from the experience of clinical trials. She proposed defining a value proposition that will incentivize industry to expand the precompetitive space to include sharing such data.

Dr. Martha Brumfield, Director of International Relations at C-Path, agreed on the importance of sharing these data but noted that there is a need to de-risk data sharing for industry. A major fear for companies is that they will be liable for how other researchers use these data if they go into the public domain. She proposed thinking about how to create a legal safe harbor for data owners to share.

IX. Regulatory Perspectives on Combination Therapy Development

Bob Temple, M.D., U.S. Food and Drug Administration

An FDA regulation in place since the 1970s stipulates that drug developers who wish to combine two drugs in a fixed combination must demonstrate that each individual drug contributes to the claimed effect. Companies seeking approval for combination therapies have typically demonstrated this with a factorial design to compare the combination to each drug in isolation.

However, the oncology and infectious diseases community have requested additional FDA guidance on development of biologically plausible combinations of *novel* drugs and, specifically, what data would be required to support the combination of two novel drugs.

The FDA recognizes the worth of efficient development of two or more drugs that have additive effects in a serious disease. Further, it is reasonable to expect that a growing understanding of pathophysiology may stimulate therapeutic approaches using combinations directed at multiple targets. In 2010, the FDA published the draft guidance “Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination.” Because the FDA has limited experience in novel-novel development, the document is high level by design, describing a general approach to deciding whether codevelopment is appropriate and to obtaining the necessary preclinical and clinical data to support the contribution of the individual drugs to the combination, which is still required under the historical regulation.

The 2010 guidance recommends four criteria for determining whether codevelopment is appropriate:

- The combination will be used to treat a serious disease.
- There is a compelling biological rationale for the combination; for example, the agents inhibit distinct targets in the same molecular pathway, target a primary and compensatory pathway, or inhibit the same target at different binding sites to decrease resistance or allow lower doses.
- A preclinical model (*in vivo* or *in vitro*) or short-term clinical study on an established biomarker suggests that the combination (a) has substantial activity and (b) provides greater than additive activity or a more durable response.
- There is a reason why the drugs cannot be developed individually; e.g., monotherapy leads to resistance or has little useful activity.

For nonclinical codevelopment, the guidance is very focused on oncology and anti-infective products because the biology of such diseases along with good animal models provide plausible rationale for a combination. It is not clear how this approach would pertain to a drug to modify AD; Dr. Temple suggested that depending on the persuasiveness of the animal model, a combination that elicits an additive or synergistic effect could be supported through the abbreviated pathway outlined in this guidance. However, there are some concerns about whether findings in animal models of AD are predictive of human results. In any case, there will always be a requirement for clinical data to support the effectiveness and safety of the combination. The expectation is that non-clinical toxicity studies would be conducted on each drug separately as usual.

The guidance next outlines the steps for clinical codevelopment. Early studies will be similar to normal procedure; however, these studies should also include PK data on the combinations. Dose-response on a relevant PD or short-term clinical endpoint should also be obtained for each component, and of great interest would be the effect of various combinations on these endpoints.

At the proof-of-concept phase, developers would need to show the contribution of each component to the extent possible and needed (given preclinical and pharmacologic data), the effectiveness of the combination, and an optimized dose or doses for Phase 3 trials. For dose

finding, the guidance encourages testing of multiple doses of both components, which is easier if there is a good marker of early response but is harder otherwise.

However, exactly what is required and what is possible in a Phase 2 will vary according to the specific circumstances. To demonstrate the range of possibilities, Dr. Temple presented three scenarios of proof-of-concept phase studies for novel-novel codevelopment.

- A factorial study could be fielded to compare Combination Drug AB to Drug A to Drug B to placebo or standard of care (if the standard of care is used, the study should be an add-on design). The study might incorporate an adaptive design so that an arm that is clearly not working could be dropped early. Acceptable endpoints could include PD or other biomarker or clinical endpoints.
- If components cannot be given individually because, for example, people would be left dangerously undertreated, it would preclude a factorial study of Combination Drug AB versus Drug A versus Drug B. In this case, the proof of concept would be based on comparison of the combination with standard of care (or placebo) or a trial of combination added to the standard of care.
- Where one drug is inactive or barely active but enhances the other, it need not be studied alone so that testing Combination Drug AB versus A versus placebo would be sufficient.

Dr. Temple concluded that it remains to be seen whether any of these scenarios are reasonable for AD. In short, if there is a dramatic effect the way forward is clear; however, a modest effect would present challenges.

The guidance states that *in vivo*, *in vitro*, and/or phase 2 studies need to “adequately demonstrate the contribution of each component to the combination” but does not say how. The hope is that Phase 2 would provide convincing evidence of the contribution of each drug on a persuasive PD endpoint so that the Phase 3 study could potentially be limited to a comparison of the combination to placebo or standard of care (given to both arms), which would translate into a significant reduction in the size of the study. However, if the contribution of each is not shown in Phase 2, Phase 3 would need to be a factorial or three-arm study to show a role for the less clear component. In all cases, studying more than one dose of the more active drug is recommended.

Dr. Temple concluded that the guidance document demonstrates some more flexibility than the original regulation; most important, evidence of a contribution can be based on data short of the usual Combination Drug AB versus Drug A versus Drug B versus placebo. However, he welcomed and encouraged developers to communicate with the division about their specific codevelopment programs. He concluded that, given the severity of AD, if a two-drug combination convincingly delayed its progression it would be difficult for the FDA to not approve such a combination.

X. Discussion

Dr. Sperling asked whether the FDA views the excessive length of trials for AD monotherapy as a sufficiently compelling rationale for codevelopment, particularly for early stages of disease.

Dr. Temple responded that the Agency is open to consider the role of problems in AD drug development such as long trial duration.

Dr. Johan Luthman, Merck, commented that one of the stated criteria for codevelopment is having preclinical or early clinical data on an established marker that demonstrate a potential for more than an additive effect; that is, a synergistic effect. He concluded that while it is easy to imagine that a combination acting on both Tau and amyloid will be synergistic, requiring synergism may pose a significant barrier to codevelopment because there is limited evidence from preclinical or biomarker models that this is achievable. Dr. Temple acknowledged that demonstrating synergy is very difficult and clarified that an additive effect would be considered sufficient. He stated that the document language will likely be revised to indicate that while achieving synergism would be ideal, it is not required.

Dr. Ben Johnson, Eli Lilly, sought guidance on the following scenario: In a Phase 3 trial with a cognition endpoint that also employs a biomarker that is questionably linked to disease progression, should the company maintain the factorial design of Drug A versus Drug B versus Combination Drug AB if they previously showed that the combination moved the marker to a greater degree than either drug alone? Dr. Temple stated that if a combination shows an effect on a plausible biomarker, even if it not known whether the biomarker corresponds to outcome, the combination study answers that question in the case where both drugs affect the same biomarker. From his perspective, the study of the combination might very well be persuasive because, after all, it does validate the biomarker. He also reminded participants that the effect size required for a factorial study would be a huge multiple of that required for a single entity.

Dr. Johnson also asked how, in a case where Drug A and Drug B work individually but not as well as the combination, the approval of either Drug A or Drug B alone would be affected. Dr. Temple expressed doubt about whether drug codevelopment could also support separate marketing of two individual drugs. The FDA would certainly want any combination to cover the range of doses that could be used, but whether they would require data on each dose is another question. He concluded that before a company could market a single drug, they would have to demonstrate that it is useful in monotherapy.

Dr. Robert Berman, BMS, asked whether, if the components of a combination and the combination itself are shown to be effective and safe, there would any modification to the requirement to show each individual drug's contribution. Dr. Temple stated that the FDA expects developers will have more limited data on the individual components and their safety than on the safety of the combination. This is appropriate unless a safety concern emerges in a Phase 3 trial of the combination; in that case, it may not be clear which drug caused the problem and this may ultimately defeat approval of the combination. It would also leave open the question of whether a lower dose of one of the components could have avoided the adverse effect. This is an inherent risk to this approach. However, given the severity of AD and the lack of treatments, demonstration of a major effect by a combination would have significant weight in the approval process even if there were safety issues.

Dr. Stephen Salloway, Brown University, posed this scenario: If two drugs individually have a modest effect that is insufficient to lead to independent approval but they have a greater effect in combination, would the Agency require a second confirmatory trial? Dr. Temple stated that the guidance is meant to address this problem; namely, that the developer would have to do a study so enormous to show the contribution of each (because the effect is so small) that it would be

unfeasible. The point of this guidance is to acknowledge that such an approach is in no one's interest. He concluded that the usual rules apply to whether a confirmatory trial is required, but if there is good Phase 2 evidence, that could be all the confirmatory evidence that is needed.

Dr. Rusty Katz sought clarification on whether, in a case where two drugs are intended to always be given together, the Agency would require nonclinical toxicity data on each drug individually. Dr. Temple stated that based on his reading of the guidance, they would require toxicity studies on both the single entities and the combination in case they have some adverse interaction. While there may be cases where studying the safety of only the combination is appropriate, he expressed a preference for knowing the safety profile of each drug individually early on as this information will be helpful in choosing dose. Working up only the combination would be complicated, forcing the developer to study multiple doses; therefore, there are also practical reasons for the usual approach to toxicity studies.

Dr. Sperling noted that in AD drug development there are some candidates both early and in late development for which dose finding is complete. She asked whether it would be a reasonable strategy to test multiple doses of the lesser known compound with a fixed dose of the drug for which more information is known all the way through Phase 3, or whether the Agency would require testing of multiple doses of each. Dr. Temple recognized the tension between what is optimal and practical. He stated that while one drug may be well known, it is not known how it interacts with the other drug, and the more data there are the better. However, if there is a reasonably likely biomarker, a fair amount work can be done in Phase 2, and certainly a developer can choose to drop a group that is not performing well. He stated that the Agency embraces adaptive designs in these early settings as the most likely pathway to finding the best dose. While there are practical limitations because it is challenging to have many doses in a big Phase 3 trial, finding the right dose is important. The FDA's position is that it is worth spending the additional money to ensure adequate coverage of the dose range. They have learned from cardiovascular drugs, for example, that a relatively small difference in dose can translate into huge differences in outcomes.

Dr. Salloway noted that in oncology, there is a precedent of testing more than two drugs and asked whether the Agency would object to combinations of more than two drugs that target multiple processes in AD using an adaptive design. Dr. Temple affirmed that the FDA has approved combinations with more than two drugs, but he clarified that the cancer combinations are not technically a fixed-dose combination so the same rules do not apply. He also raised the important but neglected issue that most new therapies are approved on the basis that when they are added to the existing therapy there is additional benefit. However, no one studies whether the original therapy is still needed with the addition of the new drug.

Mr. Allan Fox, FoxKiser, asked how the Agency could work collegially with a coalition of companies focused on AD drug codevelopment. Dr. Temple affirmed that the FDA is enthusiastic about a collaborative approach, but companies control their data and historically have not been willing to share them. However, the mood about data sharing is changing in industry, and there are success stories such as from AIDS drug development. While the Agency does not reveal privileged information, they do base their study design advice on experience, which is informed by the successes and failures of other companies. He also noted that the

agency is working collaboratively with companies to address poor follow-up rates in cardiovascular trials, which is a shared problem in that development sector. Dr. Katz added that if companies are interested in meeting to discuss how to solve problems in AD drug development in a collaborative manner, the FDA would willingly participate.

XI. Opportunities for Precompetitive Collaboration in Alzheimer's Disease

Discussion Leader: Allan Fox, FoxKiser

*Panelists: David Dilts, Ph.D., Center for Management Research in Healthcare
Owen Fields, Ph.D., Pfizer
Rusty Katz, M.D., U.S. Food and Drug Administration
Johan Luthman, D.D.S., Ph.D., Merck
Diane Stephenson, Ph.D., C-Path Institute*

This panel discussion focused on moving toward cooperation and overcoming barriers in science, business practices, and the legal environment. Industry panelists led off by presenting their perspectives on the relevant barriers and incentives for industry collaboration as well as potential models of collaboration.

Dr. Owen Fields identified several possible negative industry perceptions about cooperating on combination development. One is a concern about complex and time-consuming early development requirements that could extend into Phase 3 if there is not adequate factorial showing prior to Phase 3. He characterized this as an addressable concern with strong regulatory science, and the guidance appears to be appropriately flexible. However, there are some outstanding questions about how the guidance would be applied to AD, especially in a disease modification context. The second concern is how to address intellectual property (IP), but Dr. Fields noted the existence of successful models for overcoming IP issues.

There are two types of relevant IP. The first is confidential data/information and company “know-how,” which can be managed through an industry consortia model such as NCATS. In addition, Transcelerate, a new nonprofit company that was founded by a number of large pharma companies, as well as C-Path have addressed this IP issue for clinical conduct, clinical data standards, and data sharing. He concluded that there is no fundamental difference between codevelopment of new drugs for AD or any other disease as long as the data can be blinded and a company’s legal rights can be protected. The second IP of relevance is patents, which is of course critical to industry survival; the specific industry concern about patent issues in novel-novel drug combinations is which party owns the IP when a combination involves drugs from different companies. While this issue is very complex, patent lawyers in industry regularly address it in the form of alliances, in-licensing activities, and joint ventures, among other strategies.

Another potential concern for industry is the regulatory process for combinations; for example, two INDs versus one IND, one company providing all their IND content to another company, or the inability of the FDA to communicate with a non-owner of regulatory files. Fortunately, there are mechanisms to address these issues. For example, a company can give another company the “right to reference” their IND or drug master file, making the content completely available to FDA reviewers but invisible to the other company. In addition, the FDA is now accepting single

INDs for two compounds, reducing procedural complexity. Finally, joint development teams can be established and have been successful, even between pharma and device companies, which have very different procedures, standards, and cultures.

Dr. Luthman next reviewed the various types of collaboration models that are already used in industry. These include classical competitive partnerships between private entities, which account for 50% of drugs developed today; public-private collaboration formed through a competitive partnership between academia and industry; public precompetitive consortia that serve the entire industry, such as ADNI and CAMD; and private precompetitive consortia wherein nonprofit private groups partner with industry. There are also some novel competitive partnership models; for example, a virtual company is an IP-dependent, resource-sparing model, and there is also a model of open-source development, where a molecule is placed into an open space and anyone can bid for a spot on the program. The development team is built in the virtual world, and participants receive a percent royalty based on their contribution. He concluded that current precompetitive attempts to standardize AD diagnostics will be a good test case for whether such partnerships can be used for novel drug combination development.

The ensuing discussion developed ideas presented in the morning session and coalesced around several key themes, as described below.

Key Theme 1: The time is right to pursue combination therapy.

Alzheimer's disease is a sustained epidemic, affecting 5.4 million Americans; of the top 10 leading causes of death in the United States, it is the only one for which there are no therapies to prevent, cure, or slow the disease. The failure of two decades of effort to develop effective AD therapies is enough incentive for some in the field to consider alternatives to a monotherapy approach, which is unacceptably slow and, to date, unsuccessful. From a public health perspective, this disease meets the FDA criteria for diseases that are suitable for combination drug development. In addition to clear signals from the FDA that the agency is willing to support a combination approach, the patient advocacy community is eager to see more rapid development of effective therapies.

While recognizing the clear public health imperative to develop effective drugs, some participants who questioned whether the time is right for combination therapy. The main argument against such an approach is that the amyloid hypothesis has not been fully tested with the existing monotherapies and the field has yet to develop tools to fully test that hypothesis. Participants with this perspective contended that there is lack of strong scientific rationale for moving into combination testing until the existing monotherapies are fully tested.

However, the majority of participants supported the idea that now is the time to begin pursuing combination therapy. While there was agreement that the field has yet to adequately test the amyloid hypothesis, some participants argued that there is no empirical evidence to date that amyloid-lowering strategies alone are useful. Further, there is prima facie evidence that a patient with AD has more than just amyloid pathology. Therefore, the idea that targeting a single mechanism will knock down the disease seems implausible. One participant suggested that monotherapy testing does not necessarily need to be abandoned but that it should occur in parallel with combination therapy development in parallel.

Another rationale put forward to support combination therapy is the evidence from transgenic animals with amyloid, Tau, and inflammatory phenotypes that have augmented disease. Most AD drug development relies on single-pathology animal model, but it was suggested that the scientific evidence for combination therapy could emerge if data from various animal models with different pathologies were integrated.

Notably, while the FDA guidance focuses on novel-novel combinations, participants agreed that it is unlikely that two drugs that might be candidates for combination will be in the same stage of development. Thus, participants expressed interest in considering combinations of advanced compounds with newer drugs and even revisiting existing drugs to test them in combination. FDA representatives at the meeting emphasized that while the Agency is guided by some general principles around combination development, they have limited experience in this area and do not expect there to be a “one-size-fits-all” process. FDA participants urged developers to consult early with the FDA about how to proceed with their specific combination programs.

Key Theme 2: Collaboration is essential to the development of combination therapy.

The chance that one company owns the two or more molecules essential for a successful combination is low; thus, combination therapy development necessarily requires collaboration among industry partners. One industry participant stated that industry will be encouraged to collaborate if there is demonstration of an appropriate risk/benefit to the approach. For example, a test case that showed some tangible benefits of collaboration will compel companies to take a bigger scientific, regulatory, or intellectual property risks. One already-known value added of collaboration is the potential to decrease the amount of time required to identify and enroll patients; this is especially important for drugs targeted at earlier or even presymptomatic stages of disease. For this reason, industry participants expressed support for collaboration via a revamped clinical trials process, such as an adaptive design Phase 2 trial of combinations. Another suggestion for reengineering the trials process in a way that benefits both patients and industry is to create a national AD patient registry. FDA participants also encouraged companies to consider designing less burdensome trials with more limited data collection protocols as the sheer volume of data collected in contemporary trials is not always necessary from the Agency’s perspective and adds expense and complexity.

There was discussion of the various possible models for industry collaboration and presentation of precompetitive and competitive models including the Critical Path to TB Drug Regimens (CPTR), programs within the National Center for Advancing Translational Science (NCATS), the I-SPY trial, and consortia and partnerships from other industries were all presented as potential models for industry collaboration. However, participants did not achieve consensus on which model is the most appropriate for AD combination drug development. One industry participant suggested that there would be little incentive for companies to collaborate precompetitively because while this approach avoids IP issues, it will be challenging if the end goal is bringing a drug or drugs to market. On the other hand, a number of participants advocated for a broader definition of what activities are “precompetitive.” In particular, industry was called upon to consider data sharing as a key step toward realizing the goal of developing combination regimens. Vast amounts of historical trials data reside within companies, and companies typically do not apply internal resources to mining that data for lessons learned. Yet the success

of combination therapies hinges on a complete understanding of all of the data surrounding the individual drugs to be combined, including genomic data, biomarker signatures, and signal transduction pathways. This information is critical for decision making and modeling concepts related to dose finding and appropriate clinical settings for combinations. A legal framework that could support precompetitive and collaborative data mining of these industry trials databases for the purposes of combination drug development would be a major step forward.

Key Theme 3: Barriers to industry collaboration are formidable but resolvable.

Participants identified IP issues as a major potential barrier to collaboration; however, there are existing examples of how IP interests can be preserved within a collaborative model, even in the competitive space. For example, participants were intrigued with the template legal agreement used by NCATS for its drug repurposing program. There are also existing regulatory mechanisms that give other parties the right to reference proprietary data. FDA representatives commented that it would be difficult to develop a combination regimen with drugs from two companies without both parties having access to all of the information about the drugs involved. While it is possible to have a third party hold the IND and manage the trial, FDA participants characterized that approach as cumbersome. In general, participants agreed that they need to involve the people who have the greatest concerns about IP (i.e., industry lawyers) to present the issues and deconstruct that problem so that solutions can be identified. However, one participant cautioned the group against assuming that legal issues are the major barrier to collaboration as it is possible that there are other even more important barriers; research and data gathering are essential steps to understanding and overcoming both the known and unknown barriers.

Key Theme 4: Industry needs assurances that collaborating will not result in negative regulatory or legal consequences.

A major disincentive for industry collaboration is the fear that working together will not only lessen competitive advantages but also have legal ramifications. Thus, a major need identified by industry participants is to have an appropriate legal and regulatory framework for collaboration. Specific concerns include the following:

- Big pharma collaboration could violate anti-trust laws.
- Companies may be wary of combining their drug with another company's because of concerns that adverse effects of the combination may hamper the regulatory approval process for the drug in monotherapy.
- Industry will be concerned that if trials data are shared publicly, the company will be held liable for harm to patients based on subsequent research using their data.

Several suggestions were put forth for overcoming these concerns. First, if the Government convenes industry for a collaborative initiative, companies may share openly without fear of violating anti-trust laws. One participant suggested that the most appropriate convening body is the Assistant Secretary for Planning and Evaluation (ASPE). Second, industry needs guidance from the FDA on the impact of combination therapy testing on approval of a monotherapy. Third, if industry data sharing is a priority, then there needs to be a safe harbor that will shield companies from liability for how the data are used once they are shared.

Key Theme 5: The field needs to create a strategic roadmap for developing combination therapies for Alzheimer’s.

Lessons learned from other disease areas and even other industries demonstrate the importance of creating a roadmap to solve a complex problem. Crafting a project management approach to the problem of Alzheimer’s disease would require participation not only from scientists and regulators but also legal and financial experts in the industry. These stakeholders will need to answer several key questions: What is the major function that needs to take place? What are the goals that need to be achieved? What is the timeline? What is the current state of the field, what is the desired future state, and what is the path to the goal? What are the milestones that have to be achieved prior to reaching the ultimate deliverable? Answering these questions involves data gathering, vetting the data, creating functional models and assessment frameworks, and gathering the stakeholders to hash out the issues and deliver a product.

By the end of the meeting, participants had coalesced around the idea of holding an intensive (e.g., 3 days or longer) workshop involving government, industry, advocacy and patient groups to develop this roadmap. The invitees should reflect not only scientific expertise but also expertise in public and private policy and clinical trials infrastructure. Several participants strongly advocated that this workshop should be at the invitation of the government (e.g., ASPE) and clearly tied into the mandate of *The National Plan to Address Alzheimer’s Disease*. There should be a clearly defined outcome, deliverable, and suitable funding to ensure that the process does not recapitulate the roadmapping efforts of the NIA and other groups but builds upon them to catalyze next steps in AD drug development.

XII. Conclusion

Mr. Perry thanked the presenters and participants, ACT-AD coalition sponsors, C-PATH, and the FDA. He also thanked Dr. Katz for proposing the meeting topic and Ms. Cynthia Bens for organizing the meeting.

He concluded that this meeting suggests that the way forward in AD is a Manhattan Project–type approach with collaboration from multiple sectors. It is clear that there is an urgent need to develop new approaches in AD drug development and to incentivize collaboration. There are encouraging precedents in other disease areas for reengineering the clinical trials process into a more efficient and productive system as well for industry setting aside competitive concerns to tackle a public health crisis. The next step for the field is to come together through an intensive, consensus-building process and generate a roadmap for reaching the shared vision of treating and preventing AD.