API ADAD Colombia: Baseline Data Sharing Program

Alzheimer's Prevention Initiative

In 2010, Banner Alzheimer's Institute (BAI) established the Alzheimer's Prevention Initiative (API) to help launch a new era in Alzheimer's prevention research, accelerate the evaluation of promising prevention therapies, and find and support the approval and availability of ones that work as soon as possible[1-2]. Led by Drs. Eric Reiman, Pierre Tariot, and Jessica Langbaum, API includes potentially label-enabling prevention trials of investigational Alzheimer's disease (AD)-modifying treatments in cognitively unimpaired persons at genetic and/or biomarker risk using new cognitive composite and/or clinical endpoints, better tests of the amyloid hypothesis than failed trials in later stages of the disease, a strategy to clarify the roles of biomarkers in the evaluation and accelerated approval of prevention therapies, unusually large registries and innovative programs to support the identification and enrollment of interested participants in these and other trials, and commitments to providing a public resource of baseline and post-trial data[3-9].

API trials with plans for data sharing include 1) the API Autosomal Dominant AD (ADAD) Colombia Trial of the anti-oligomeric amyloid-β (Aβ) antibody crenezumab in cognitively unimpaired 30-60 year-old Colombian presenilin 1 (PSEN1) E280A mutation carriers and non-carriers (including those with a positive or negative Aβ PET scan) from the world's largest ADAD kindred (clinicaltrials.gov identifiers NCT01998841 [for the overall trial] and NCT03977584 [for the subsequent tau PET sub-study])[10]; 2) API Generation Study 1 of the recently discontinued BACE inhibitor umibecestat (also known as CNP520) and the active immunotherapy CAD106 in cognitively unimpaired 60-75 year-old apolipoprotein E (APOE) ε4 homozygotes (including those with a positive or negative Aβ PET scan) (NCT02565511)[11]; and 3) API Generation Study 2 of the recently discontinued BACE inhibitor umibecestat in cognitively unimpaired 60-75 year-old APOE ε4 heterozygotes with a elevated brain amyloid as well as APOE ε4 homozygotes (NCT03131453)[11]. The design and size of these trials were informed by brain imaging and cognitive studies conducted by the investigators and their colleagues in PSEN1 E280A mutation carriers and non-carriers and in cognitively unimpaired APOE ε4 homozygotes, heterozygotes, and non-carriers.

The API ADAD Colombia Trial is a public-private partnership led by BAI, Dr. Francisco Lopera and his colleagues at the Grupo Neurociencias de Antioquia (GNA) (part of the University of Antioquia and the main study site), Genentech/Roche, and the National Institute on Aging (NIA). It has been supported by NIA (grants RF1 AG041705 and R01 AG055444), philanthropic contributions to the Banner Alzheimer's Foundation, and Genentech/Roche; and it is described in more detail below.

Generation Study 1 is a public-private partnership led by BAI, Novartis, Amgen, and NIA with support from NIA (grant UF1 AG046150), philanthropic contributions to the Banner Alzheimer's Foundation, Genentech, and Roche. Generation Study 2 is a public-private partnership led by Novartis, Amgen, and BAI with support from Novartis, Amgen and philanthropic contributions to Banner Alzheimer's Foundation.

API and its related programs are supported by NIA, Alzheimer's Foundation, NOMIS Foundation, FBRI, GHR Foundation, Alzheimer's Association, Flinn Foundation, other contributors, Colciencias, and our industry partners.

Data Sharing and Risk Mitigation

After the API ADAD Trial was funded by NIA in 2012, API leaders, BAI, Genentech/Roche, and their colleagues forged a precedent-setting agreement to share trial data and biological samples within 12 months after the trial is over. This precedent was followed by similar agreements to share trial data from

the API Generation Program, Dominantly Inherited Alzheimer's Network-Therapeutic Unit (DIAN-TU) study, and A4 study after those trials are over. Since then, the Collaboration for Alzheimer's Prevention (CAP), which includes leaders from FBRI, FDA, the Alzheimer's Association, and several prevention trials (including API, DIAN-TU, the A4 Trials Program, and TOMMORROW), articulated principles for sharing baseline or screening data within a year after the last participant is enrolled in the study and sharing trial data and some of the biological samples after the trial is over—principles that could be applied to other clinical trials and observational studies[12]. The principles call for data and sample sharing that would benefit the field while protecting research participant anonymity, confidentiality, and well-being, clinical trial integrity, regulatory approval chances, and availability of effective treatments for our vulnerable populations.

We took a deliberate approach to development of the API ADAD Colombia Trial Baseline Data Sharing Program in order to minimize potential research participant and clinical trial risks: 1) Since the paradigm for sharing baseline data in a potentially label-enabling clinical trial had not yet been established, we vetted data sharing approaches that would minimize risks to research participant anonymity and confidentiality, and clinical trial integrity. 2) Since most ADAD kindred members did not wish to receive information about their genetic risk and a genetic counseling and risk disclosure paradigm for ADAD had not been established in Colombia, unimpaired members of the PSEN1 E280A kindred did not know whether they are a mutation carrier or non-carrier, our double-blind trial was designed to include carriers who were randomized to active treatment or placebo and non-carriers who were matched for age at screening and assigned to placebo under double-blind conditions, and we planned to develop, test, and provide genetic counseling and risk disclosure for interested PSEN1 E280A kindred members by the time the trial was completed. Special efforts have been required to help ensure that shared data and resulting abstracts, presentations, and manuscript do not inadvertently disclose our participants' genetic risk. Moreover, this information could theoretically influence a person's cognitive performance, as well as affect clinical ratings and thus threaten trial integrity. 3) We initially considered the general (post-trial) data sharing approach espoused by the United Kingdom Anonymisation Network[13], which supports data sharing while helpfully laying out a variety of considerations for those attempting to do so. We vetted strategies used by DIAN to share observational data, baseline data from the DIAN-TU, and screening data from the A4 Trial. We pressure-tested potential threats to inadvertent genetic risk disclosure, anonymity, confidential, and trial integrity, and developed ways to minimize them. 5) We ultimately adopted the data sharing model used in DIAN's observational study and recommended for use in the DIAN-TU study, and we are grateful to our DIAN colleagues for sharing details of their data sharing program. 6) We incorporated a procedure by which our industry partner (Roche) would quickly review data sharing requests and resulting abstracts, presentations, and manuscripts to assess and mitigate risks to inadvertent genetic risk disclosure, anonymity, confidentiality, and trial integrity, and we secured support from Roche for our baseline data-sharing program. Our baseline data-sharing program reflects our commitment to the data sharing principles we and our colleagues articulated in CAP[12], as well as NIH data sharing policies[14]. Since there will be much to learn about the optimal ways to share baseline data, the baseline data sharing program may evolve over time.

The Colombian PSEN1 E280A Kindred and API ADAD Colombia Trial

To date, researchers have identified about 275 rare mutations of the presenilin 1 (PSEN1), presenilin 2 (PSEN2), and amyloid precursor protein (APP) genes associated with ADAD[15]. Most of the mutations appear to be associated with a virtually certain risk of developing AD, and carriers develop the pathophysiological, biomarker, and clinical features of AD at unusually young ages[15-18]. The Colombian PSEN1 E280A kindred is the world's largest and best characterized ADAD kindred[18]. Mutation carriers in this kindred develop mild cognitive impairment (MCI) and dementia due to AD at the respective median ages of 44 and 49[15]. Like other ADAD mutation carriers, they develop characteristic brain imaging and fluid

biomarker measurements of Aβ plaque and tau tangle burden, decline in the cerebral metabolic rate for glucose (CMRgl), and regional brain atrophy starting more than 25 years before the onset of dementia. Dr. Lopera and his colleagues have been studying this kindred for more than 20 years[15]. With support from API, their Colombian API Registry has now enrolled nearly 6,000 living kindred members, descended from a common ancestor, and including nearly 1,200 living PSEN1 E280A mutation carriers[8].

In 2012, BAI, GNA (part of the University of Antioquia), Genentech/Roche, and the National Institute on Aging (NIA) announced the first NIA-funded prevention trial of an investigational anti-amyloid-β drug (RF1 AG041705). Launched in 2013, the API ADAD Colombia Trial (NCT01998841) is a 5-8-year placebo-controlled prevention trial of the investigational anti-oligomeric Aβ antibody therapy crenezumab in cognitively unimpaired PSEN1 E280A kindred members within 15 years of their median age at MCI onset. Mutation carriers were randomized to crenezumab or placebo, non-carriers receive placebo only, and participants will continue to be studied double-blind conditions until the last participant enrolled has completed the 60-month visit. The primary outcome is change in the API ADAD Composite Cognitive Test Score from baseline to week 260. Secondary outcomes include time to progression to mild cognitive impairment/ dementia; changes in dementia severity, memory, and overall neurocognitive functioning; and changes in selected biomarkers. Safety and tolerability are assessed.

365 cognitively unimpaired 30-60-year-old volunteers were consented and 252 were enrolled in the trial, including 169 mutation carriers and 83 non-carriers. The trial includes baseline, 24-month, and 60-month florbetapir (Aβ) PET, fluorodeoxyglucose PET, and MRI scans, additional safety MRI scans, blood samples and CSF samples in those who consent to a lumbar puncture. With the advent of tau PET methods, it also includes optional mid-trial and end-of-trial GTP1 (tau) PET. Enrollment in the trial closed in February 2017, and the trial is expected to be completed by mid-2022. The article describing the trial methods is available here[10].

When the trial is completed, we will clarify the extent to which a treatment's biomarker effects are associated with a clinical benefit, information that is needed to clarify the use of biomarkers as surrogate endpoints in future prevention trials under regulatory agencies' accelerated approval mechanisms. Since all of the trial participants were cognitively unimpaired at baseline, and more than half of the carriers did not yet have a "positive" baseline Aβ PET scan, the trial offers a better test of the amyloid hypothesis than those in later preclinical or clinical stages, as well as a chance to explore differential treatment effects in carriers with a positive or negative Aβ PET.

Snapshot of baseline trial data

Baseline trial data have been transferred to a small team of analysts at Banner Alzheimer's Institute (BAI) in Phoenix, Arizona. The data set was identified by our collaborating partners' clinical scientists based on hypotheses and analyses that had been proposed in advance of the transfer. The data set may expand over time as we and others formulate new hypotheses.

The baseline data currently include:

- Demographic information
- Clinical ratings and cognitive test scores
- Florbetapir (Aβ) PET, FDG (CMRgl) PET, volumetric MRI, and other MRI scans
- PSEN1 E280A and APOE genotypes.
- (Since GTP1 (tau) PET scans will be initiated in the middle of the trial and CSF and blood-based assays have not yet been performed, those data are not available at this time.

To protect the participant privacy and clinical trial integrity, only a small subset of the BAI analysis team ("firewalled" from the study team and other analysts) has access to the genetic information, with

the rest of the team performing analyses without this information. This step guards against unveiling genetic information linked to any individual participant.

We have shared a test data set on GAAIN (https://www.gaaindata.org/partners/online.html) and our trial team has begun to perform analyses[5]. Baseline data from multiple sources were shared (July 2018) from 242 trial participants, including 167 mutation carriers and 75 non-carriers, who were matched for age range to protect participant confidentiality.

We wish to provide a shared resource of baseline data to investigators, whether or not they are API ADAD Colombia trial collaborating partners (see below). As is the case with our DIAN partners, who have generously allowed us to use their data sharing processes as a model, our intent is to follow the principles of Productivity (with recognition of the investigator who develops a research idea and does the work to publish it), Transparency, Fairness, and Inclusiveness.

Overview of the baseline data sharing process

Our clinical science team will partner with interested researchers to define and agree on which analyses to conduct and what data to request. BAI's firewalled data analysis team and Roche's risk assessment team will then perform an assessment of risk and, when risk is considered acceptable, create a file to share with the requesting investigator. After a presentation or paper is drafted, we will perform a second risk assessment prior to approving the materials for publication or presentation.

Investigators who receive trial data must agree to share their abstracts, presentations, and manuscripts in advance, mainly to ensure that the reports will not lead to inadvertent genetic risk disclosure. For example, reports should not include figures or findings that could cause research participants or family members to determine their PSEN1 E280A carrier or non-carrier status based on their particular age or other identifying characteristics.

Initial application

1. All data requests should be submitted in writing via the API ADAD Colombia Trial online resource request system using the attached forms and emailing them to: APIData@bannerhealth.com.
2. Written requests will include the following:
    a. Request Form
        i. Investigator affiliation
        ii. Contact information
        iii. Funding support (if any)
        iv. A brief description of the project, including specific aims, hypothesis, characteristics of the data required for analysis, and proposed analysis plans.
    b. NIH biosketch or CV with similar information.
3. All materials must be written and submitted in English.
4. Investigators requesting data will be required to sign a data use agreement before receiving any data files. The investigators and their colleagues will be required to adhere to the agreement, which includes important stipulations.
5. In order to guide your request, please refer to our methods paper and data dictionary as well as other publications below.

Next steps in the process

1. The number, type and disposition of requests will be tracked by the BAI analysis and administrative teams, a data sharing report will be generated for progress and final reports to the NIA and resulting lists will be posted on our website. In order to avoid overlapping effort, requesting investigators are encouraged to review current analyses on the API ADAD Colombia Trial request website.
2. Once requests for data are received, they will be checked for completeness and then reviewed by the API ADAD Colombia Trial Data Sharing Review Committee as well as Risk Assessment teams at Banner and Roche for:
    - Feasibility
    - Scientific merit
    - Investigator qualifications
    - Alignment with goals of the API ADAD Colombia Trial program
    - Risk to the integrity of the ongoing trial
    - Risk to participant confidentiality or privacy
    - Burden on API ADAD Colombia Trial program staff
3. The standard turnaround for a review is expected to be up to 30 days.
4. If the request is approved, and the requesting investigator has returned the data use agreement, the BAI analysis team will create a customized data file. The risk assessment team(s) will review it and, once approved, it will be sent to the requesting investigator.
5. In ambiguous cases, a call or calls with our team will be scheduled earlier to clarify any issues.
6. If one of our researchers believes it would help to communicate with you about your data analysis plan by email or phone, we will let you know. In addition to privacy protections, we will do our best to provide input that might be helpful to your analysis plan.
7. If the request is denied, the applicant will be provided a brief explanation as to why this was the case.
8. After a presentation or paper is prepared, the Banner and Roche clinical science and risk assessment teams must review and approve it.

Obligations incurred by requesting investigators

1. As noted below, the API ADAD Colombia Trial Data Sharing Review Committee must approve all abstracts, presentations, and manuscripts resulting from the API ADAD Colombia baseline data prior to submission or presentation.
    a. The requesting investigator may be asked to offer joint authorship for selected API Colombia team members that meet ICJME authorship criteria as determined by the API ADAD Colombia Trial Data Sharing Leadership Team.
    b. The collaborating partners leading the API Colombia Trial (Roche, Banner Alzheimer's Institute and University of Antioquia) reserve the right not to publish results that potentially conflict with the privacy of the participants, threaten trial integrity or do not meet scientific merit criteria as determined by the API ADAD Colombia Trial Data Sharing Review Committee.
    c. For more details, please see "Publication Policy and Obligations."
2. The requesting investigator shall not give data shared from the API ADAD Colombia baseline data sharing process to third parties without that party also being included in the data sharing request proposal and executing a data use agreement.

3. The requesting investigator shall not attempt to identify individual participants in the API ADAD Colombia Trial.
4. The API ADAD Colombia Trial Data Sharing Leadership Team reserves the right to decline any analysis request. Roche reserves the same right, in cooperation with the Data Sharing Leadership Team.
5. Subject to the above, the requesting investigator and the collaborating partners leading the API Colombia trial shall have the right to use the shared data only for the approved analyses.
6. The collaborating partners shall have the right to use the results arising out of the analysis of the shared data for all purposes.

Publication Policy and Obligations

1. Should the requesting investigator intend to submit results from the API ADAD Colombia baseline data sharing process for publication at any time, the recipient agrees to notify the API Data Program Manager (APIData@bannerhealth.com) with details including:
    a. Intended publication source
    b. Any related funding
    c. A copy of the material as intended for publication (final draft).
2. API ADAD Colombia Trial Data Sharing Review Committee will review the submission for publication within 30 days in order to assure that the data, acknowledgements, authorship and content meet a minimum standard. Such publications require compliance with National Institutes for Health (NIH) public access policies[8].
3. Acceptance of API ADAD Colombia trial baseline data obliges the recipient to cite/reference the NIA grants in any presentation or publication that may result from this research. API reports productivity derived from our resources to the funding agency, the NIA. Specifically, the following language must appear in acknowledgments of all publications using API ADAD Colombia trial resources:
    a) "Data collection and sharing for this project was supported by API funded by the National Institute on Aging (RF1 AG041705, AG055444). Funding was also received from Genentech/Roche, Banner Alzheimer's Foundation, Forget Me Not Initiative, Nomis Foundation, and the Colciencias (grants: 1115-408-20512, 115-408-20543). We acknowledge the altruism of the participants and their families and contributions of the API ADAD Colombia research and support staff at GNA and each of the participating sites for their contributions to this study."
4. Acceptance of API ADAD Colombia trial baseline data sharing obliges the recipient to agree to adhere to ICJME authorship criteria. This may result in inclusion of certain authors from the trial team, as determined by the API ADAD Colombia Trial Data Sharing Leadership Team, who contribute to the final analyses by:
    a. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
    b. Drafting the work or revising it critically for important intellectual content; AND
    c. Final approval of the version to be published; AND
    d. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

5. All communications regarding the API ADAD Colombia trial data that may be classified as press releases, interviews or public web site postings must be reported to the API Data Program Manager (APIData@bannerhealth.com) before they appear or are presented.
6. Should funding result from this research now or in the future, please notify the API Data Program Manager (APIData@bannerhealth.com) with details (grant title, sponsor, number, dollar total, and dates) so that API may report productivity derived from our resources to NIA.

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