

EPAD

European Prevention of
Alzheimer's Dementia Consortium



EPAD Proof-of-concept Study

Value Proposition for Prospective
Compound Nominators

Fall, 2015

www.ep-ad.org

EPAD Goal

The European Prevention of Alzheimer's Dementia (EPAD) project aims to develop an infrastructure and study protocol that efficiently enables the undertaking of adaptive, multi-arm Proof-of-Concept studies for early and accurate decisions on the ongoing development of drug candidates, drug combinations, or other interventions for the secondary prevention of AD dementia.



Key Issues With *Traditional* Phase 2 Designs in AD

Traditional Phase 2 AD trials have yielded suboptimal results at high cost

1. Incomplete Data

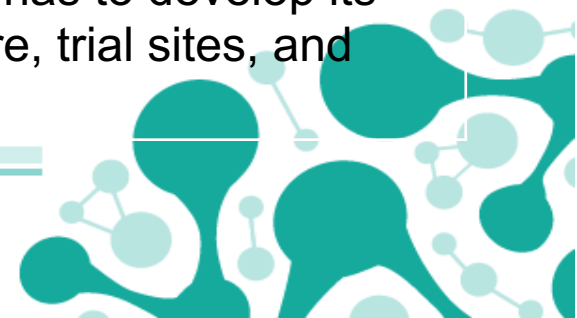
Historically, inadequate information about the clinical effects at the end of Phase 2 do little to de-risk Phase 3

2. Getting Patients

Finding the right trial subjects is challenging, costly, and time-consuming using traditional recruitment methods

3. Time & Expense

Costs are driven up by the need to conduct large and lengthy trials to improve information gathering; each company has to develop its own protocol, infrastructure, trial sites, and recruitment plan



The EPAD standing adaptive trial addresses the limitations of a traditional Phase 2 AD trial to deliver superior data faster at significantly lower cost

1. Robust Data

EPAD studies new drugs in a well-designed Phase 2 PoC trial with clinical endpoints prior to Phase 3, utilizing the power of adaptive design and Bayesian statistics

2. The Right Subjects On Demand

EPAD provides access to subjects with biomarker evidence of AD pathology who are already participating in a trial readiness cohort

3. Trial Efficiencies

EPAD's standing platform and established infrastructure deliver rapid, streamlined, high-quality study execution at lower cost on a condensed timeline

1. Robust Data

Utilizing the power of adaptive design and Bayesian statistics to improve efficiency, mitigate risk, and improve success

- Advantages of a Bayesian adaptive clinical trial design for Phase 2
- Additional advantages of participating in a standing trial through the IMI-EPAD consortium

The Bayesian adaptive design allows the trial to be more efficient, use fewer subjects, and therefore leads to stronger conclusions faster

- Frequent interim analyses for trial adaptation lead to faster decision-making with fewer subjects
 - Adapting the randomization ratios leads to more data on effective doses and dose-response
 - Recruitment to a given treatment arm can be adapted to increase/decrease the number of subjects in a specific subpopulation depending on efficacy and/or safety signals in that population
 - Prespecified decision rules permit early stopping for success or futility, to accelerate drug development or conserve resources for other projects
- Bayesian statistics improve trial efficiency
 - Utilize all available data at each interim analysis to increase power
 - Continuously updates longitudinal model to enhance predictive power as learning progresses

Source: Berry Consultants.

Further advantages of a standing trial platform

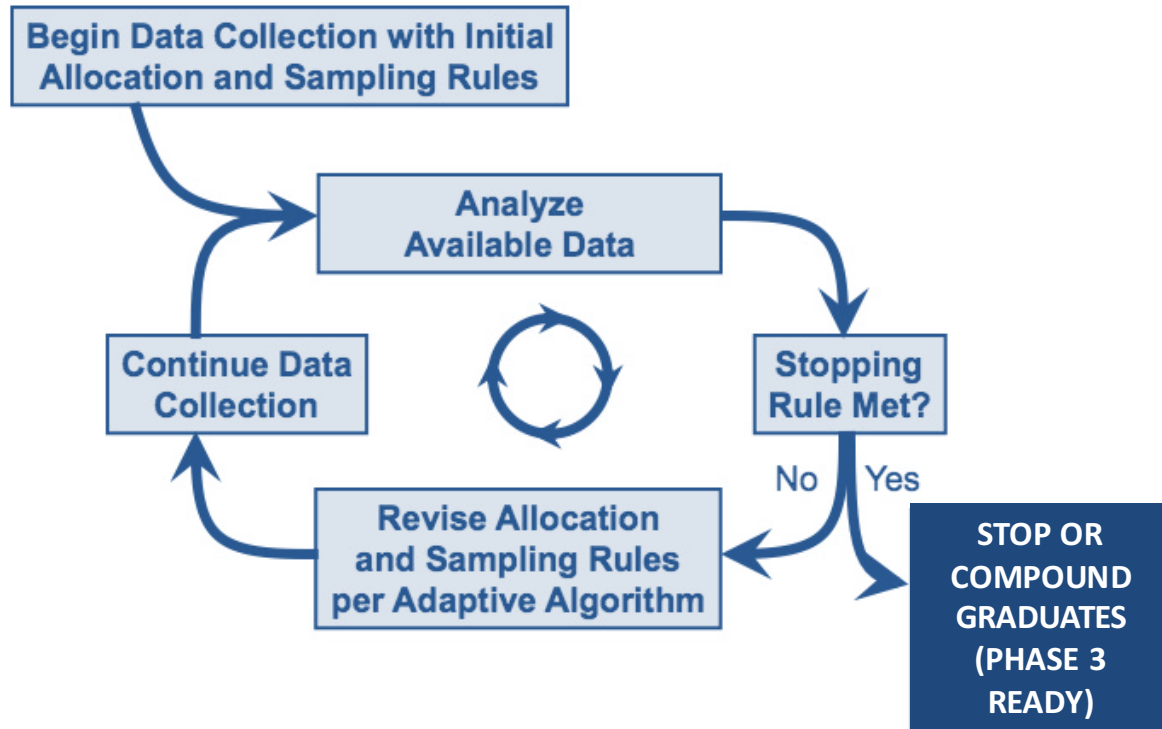
- Possibility for sharing of placebo subjects across treatment arms reduces the overall sample size of the trial
- Access to more data to validate novel biomarker and clinical assessments
- Bayesian statistics provide a formal mathematical method for combining prior information with current information at the design stage, during the conduct of the trial, and at the analysis stage, resulting in a continuous improvement in the efficiency of the trial design

“Downstream” benefits

- More efficient design, using fewer subjects, more and earlier opportunities for decision-making, and increased power of analyses makes possible a robust Phase 2 proof-of-concept in which clinical (not just biomarker) success can be achieved at reasonable cost, mitigating the risk of Phase 3 failure
- Selection of study populations for Phase 3 are based on realistic probabilities of success rather than on unreliable post-hoc subgroup analyses
- More efficient use of subjects leads to better acceptance by IRBs, investigators, and patients

Bayesian Adaptive Trial Summary: The *Better* Way to PoC

Unlike a static Phase 2 design, the Bayesian adaptive model allows the trial to be more efficient, use fewer subjects, and result in stronger conclusions



Source: Berry Consultants.

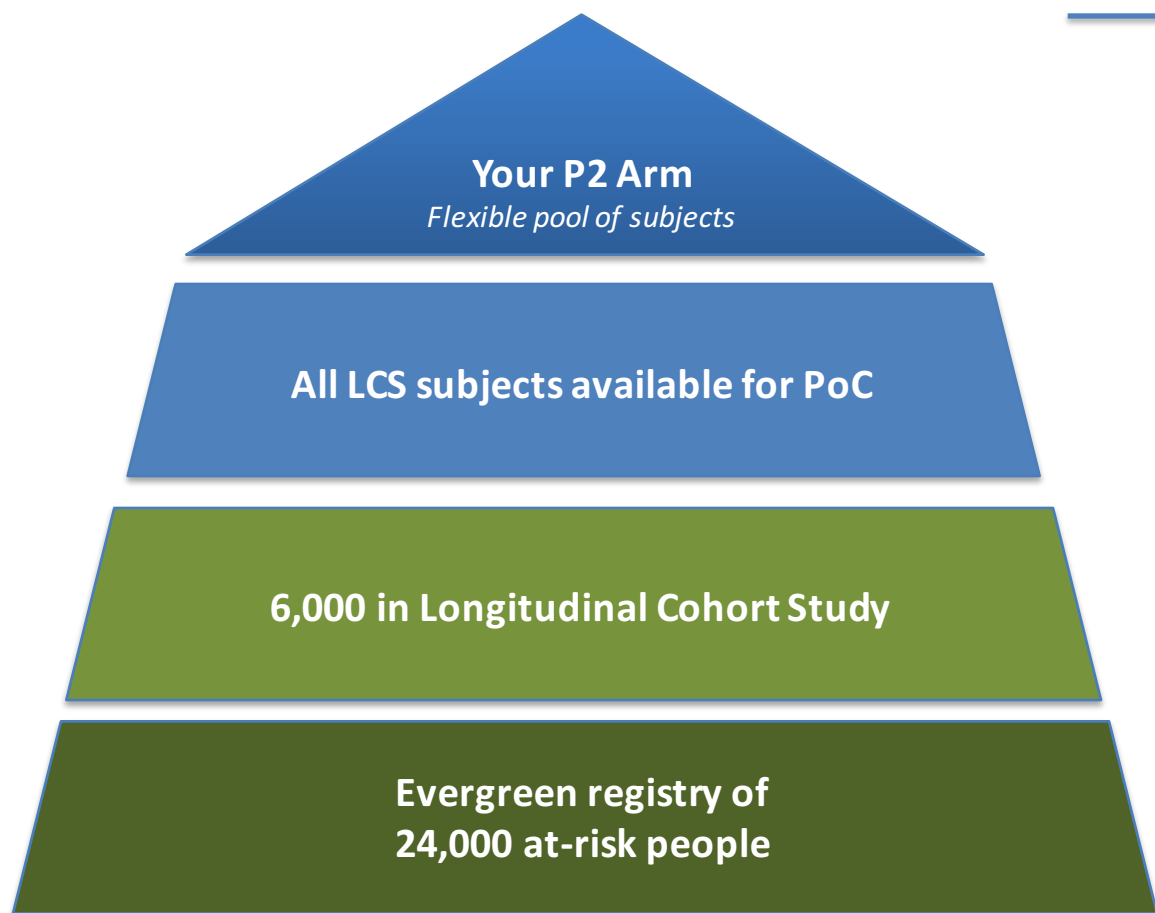
2. Subject Recruitment The Right Patients... *On Demand*

EPAD accelerates subject access and trial enrollment by providing a pre-identified, trial-ready cohort of 6,000+ subjects for quick, targeted recruitment

- Enrollment into the PoC is faster and less costly
 - Faster and more predictable enrollment because the Longitudinal Cohort Study (LCS) provides stable, ongoing access to an at-risk population with **biomarker evidence of AD prior to the development of dementia**
 - Lower cost of enrollment due to fewer screen failures because potential study subjects already well-characterized by **genetics, biomarkers, and clinical status**
- Subjects culled from registries and cohorts are already **followed longitudinally** which provides multiple advantages
 - Increased adherence and decreased drop-out rates
 - Individual natural history data can be used as a baseline to provide greater power to detect changes in the clinical course trajectory due to treatment



Subject Recruitment: How It Works



EPAD accelerates subject access and trial enrollment by providing a pre-identified, trial-ready cohort of 6,000+ subjects for quick, targeted recruitment process



3. Trial Efficiencies

Standing platform trial and ready-to-go infrastructure delivers more accurate data at lower cost and with more predictable timelines, improving overall drug development planning

Trial Efficiencies: Ready-To-Go Phase 2 Infrastructure

- **Protocol**

SAP, analysis algorithms, longitudinal data model, programs for running simulations, IVRS for adaptive randomization

- **Agreements**

CRO and other vendor contracts already in place; IRB approvals; regulatory feedback

- **Resources**

Pre-established, experienced, and well-trained Trial Delivery Center site network

Trial Efficiencies: A Quicker Outcome Lowers Costs

***Speeding clinical trials:
Less time required from start up to PoC leads to lower
management costs and higher recruitment rates***

ILLUSTRATIVE EPAD TIME/COST BENEFIT

	PATIENT RECRUITMENT	LOWER SCREEN FAILURE	MANAGEMENT COSTS	INFRA STRUCTURE
P2 CURRENT	~0.15 subjects/site/month	75%+ SFR	PM and medic time for 12+ months	Build from scratch
EPAD POC	3-4 subjects/site/month	< 25% SFR	PM and medic time for less than 6 months	Already in place
POTENTIAL EPAD COST BENEFIT	4-5x faster (while utilizing fewer than 1/3 the sites)	~50%+ SFR benefit	6-12 months trial management cost savings	Time and money

Trial Efficiencies: Standardization Benefits

- Uniform training across sites
- Standing trial with drugs cycling in and out allows continual gains in expertise and reduces variability in assessment
- Standardized study quality surveillance
- Agreed regulatory process and acceptability, with plans to discuss the following with CHMP
 - Potential for PoC trial results to be considered supportive for registration
 - Potential for seamless transition into Phase 3



Trial Efficiencies: Broad Scope For Flexibility

- Large array of standardized endpoints available that can be flexibly chosen for individual drugs
- Potential to tailor for individual drugs
 - Broad range of available subjects from asymptomatic through symptomatic without dementia
 - Inclusion of ApoE4+ and – subjects for selection or stratification
 - Stopping rules for success or futility, sample sizes, durations of treatment, and safety assessments
- Potential for studies of combination therapy

4. Other Benefits

Access to the EPAD community provides many benefits for your Phase 2 trial and beyond

Benefits of Collaboration

More Ideas, Better Science

Streamlined way to coordinate, communicate, and maintain engagement with patient and caregiver advocacy groups and other key stakeholders



Source: HealthKnowledge..

Joining The EPAD Trial Platform *The Better Way To PoC*

The EPAD standing adaptive trial addresses the limitations of a traditional Phase 2 AD trial to deliver superior data faster and at lower cost

Access To World AD Experts 35+ Partners

EFPIA Members

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Sanofi-Aventis
Novartis
Boehringer Ingelheim
Eli Lilly
Lundbeck
Takeda
AC Immune
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Amgen
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Karolinska Institutet
Stichting VU-VUmc
University of Cambridge
Medical Research Council Biostatistics
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Cardiff University
Centre Hospitalier Universitaire de
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Institut National de la Santé et de la
Recherche Médicale
University of Leicester
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Aridhia

Others

Alzheimer's Europe
Synapse Research Management Partners
Berry Consultants
IXICO Technologies
Quintiles

