European Platform to Facilitate Proof of Concept for Prevention in Alzheimer's Disease (EPOC-AD)

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Need for public-private collaboration

- The cost and challenges of establishing AD prevention strategies make a strong case for a public private partnership in this area. It is unlikely that any one party alone would be able to provide the necessary investments to establish an efficient POC development paradigm.

- The challenges of developing prevention approaches in AD include identifying subjects at risk, developing efficient study designs, constructing appropriate clinical endpoints, including relevant biomarkers and establishing methods for prevention.

- The risks associated with proof of concept trials for the development of therapeutics for AD prevention are best addressed through a collective effort that minimizes the utilization of patient, health professionals and financial resources through duplicative efforts on the part of individual pharmaceutical companies.
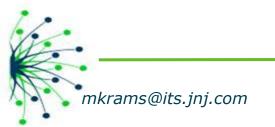
Need for public-private collaboration

- Coordinate and orchestrate already existing natural history cohorts studies to contribute to IMI-EPOC AD

- Build a "trial-ready cohort" with run-in data acquisition

- Expand "trial-ready cohort" into "longitudinal natural history study" with relevant biomarker observations

- Develop a scaffold to include subjects participating in longitudinal natural history study

- Establish an international collaborative group for advancing adaptive trials in preclinical to early AD

Objectives of the full project

- To create a novel clinical trial process to establish POC for prevention of AD treatments, allowing the continuous testing of multiple different regimens, involving a shared and rotating placebo population to ensure that a greater percentage of participants receive investigational treatments.

- The approach will involve an adaptive trial design for comparisons across investigational options, permit disease modelling , shared processes and centralized resources. A similar model (ISPY-2) has proven successful in the development of oncology therapies (Barker et al., Clin. Pharmacol. Ther, 2009).

- The overarching goal is more efficient and rapid learning using an iterative approach about which regimens are better for which patients (i.e., biologically important subtypes which also permits simultaneous assessment of biomarkers of disease subtype and/or progression).

Objectives of the full project

- Directly comparing diverse treatments to a common placebo reduces the number of participants who must be treated with placebo and permits efficient determination of which investigational treatment arms should be explored for which patients and which arms should be abandoned and/or re-positioned for a different subgroup.

- The initiative will create a readiness registry of potential participants who will be sufficiently characterized in advance of the trial. This will increase the efficiency of trial recruitment and the likelihood that the population will be able to optimally answer the questions posed.

- Individuals at risk for developing Alzheimer's disease should be studied and characterized prior to entering a trial such that when individuals reach certain pre-specified criteria, they will be eligible for trials.
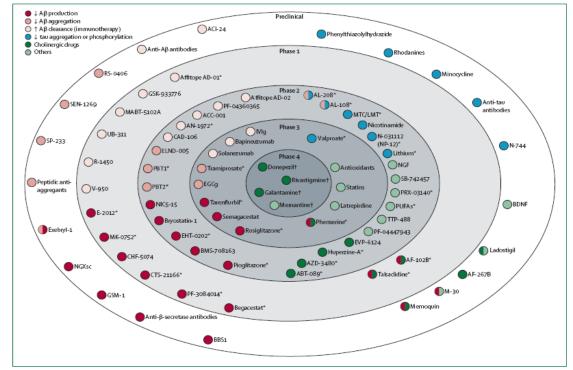These pre-qualified participants (based on the progression of their illness and/or biomarkers) will have a reduced likelihood of receiving placebo treatment and an increased chance of receiving treatment with multiple investigational agents alone or in combination.
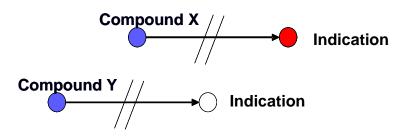
Objectives of the full project

Figure: Drug development in Alzheimer's disease
Drugs being investigated for Alzheimer's disease therapy, reported according to the most advanced phase of study and main therapeutic properties (including data from studies in vitro and animal models). Aβ=amyloid β. BBS1=anti-β-site antibodies. BDNF=brain-derived neurotrophic factor. EGCg= epigallocatechin-3-gallate. IVIg=intravenous immunoglobulin. LMT=leuco-methylthioninium. MTC=methylthioninium chloride. NGF=nerve growth factor. NGXsc=NGX series compounds. PUFAs=polyunsaturated fatty acids. GSM=γ- secretase modulator. RCT=randomised controlled trial. *RCTs in Alzheimer's disease not ongoing. †Drugs approved for the treatment of Alzheimer's disease.

Move from a "siloed" approach of individual compounds to an integrative combination approach

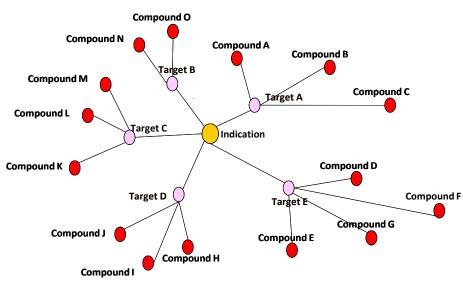# Objectives of the full project

Desired approach is multi-dimensional

Mechanisms → Targets → Molecules →

	Aβ Production	B-secretase
Amyloid pathology		γ-secretase
		A-secretase
		Oligos/antisense (future)
	Aβ Removal	Antibodies
		Vaccines
	Aggregation	Antibodies
		Chelators
	Distribution	LRP
		RAGE
	Degradation	Neprilysin
Tau pathology	Microtubule destabilization	
	Aggregation	
	Phosphorylation	Kinases
	Spreading	Antibodies
Neurodegeneration		
Autophagy		
Cognitive deficits		

Pre-competitive nature

- A public-private partnership is proposed to promote more efficient clinical trial designs and execution of clinical trials aimed at preventing AD dementia.

- The plan would create a precompetitive space to enable collaboration for optimizing patient selection, clinical trials methodologies, and candidate therapies, as well as conducting adaptive clinical trials that will produce the greatest likelihood of success.

- A consortium of industrial, governmental and academic partners will be formed to advance :
  1) a registry of individuals at risk ready to participate in clinical research,
  2) a longitudinal observational cohort of individuals at risk that will provide deep insights into disease course and trajectory,
  3) a program of continuous adaptive trials to establish POC (Proof of Concept) testing of investigational compounds for the prevention of AD dementia.

- Although all general learnings will be shared, compound specific information remains intellectual ownership of the company, based on appropriate IP and legal framework.

Expected impact on the R&D process

- The continuous learning cycle that will be created in this program will adaptively incorporate innovations and learning regarding endpoints and biomarkers that may emerge within, or external, to the project.

- The rapid recruitment of available subjects from the longitudinal observational cohort to the clinical trial component of the program, coupled with the adaptive nature of the clinical trials and utilization of a common control group, will reduce the time needed to evaluate individual treatment arms, while simultaneously allowing a greater number of compounds to be tested.

- Multiple industrial and public partners should be able to enter their candidate therapies in the platform. That will in turn enable within and across class treatment evaluations so best candidates for large scale confirmatory trials can be identified.

- In general, the approach would result in a cost and time saving for POC testing of compounds and compound combinations for the prevention of AD.

Suggested architecture of the project

- Applicant Consortium is expected to address all research objectives and make key contribution to the defined deliverables in synergy with EFPIA consortium

- The proposed architecture is just an example; different innovative project designs are welcome, if properly justified, including different sizes for the registry, longitudinal study and randomized clinical trial or a different organization of the work packages.

- Proposed architecture should provide the first five year grant period research plan.
  - The development of a registry of 24,000 subjects should be initiated immediately after the start of the project and accrue over 2 years.
  - From this registry, it is estimated that there will be a prospective longitudinal cohort study of an estimated 6000 consenting subjects who will be followed for > 6 months and offered the further opportunity following consent to be screened and randomized into a rolling adaptive randomized clinical trial (~1500 subjects).
  - The first subject randomized into the interventional randomized clinical trial (RCT), having had their longitudinal course sampled in the longitudinal cohort study, should begin ideally within 1 year from project start with interventional trial results being evaluated thereafter throughout the 5 year funding period.
  - Both the prospective longitudinal cohort and interventional studies may extend beyond the 5 year grant period (via additional mechanisms, including a possible expansion into future Calls that should be considered while building the business case and will be further developed at the Full Project Proposal stage).

Expected contributions of the applicants

- **Work Package 1: GOVERNANCE TO ADDRESS THE SCIENTIFIC CHALLENGES**

  All key expertise areas necessary to deliver on all scientific challenges, including:
  - Expertise with regard to AD genetics, biomarkers, and neuropsychological and clinical assessments that may be useful for patient selection and study endpoints.
  - Scientific rationale for selecting compounds and combinations to be tested.
  - Innovative approaches to the adaptive clinical trial process.

- **Work Package 2: ELABORATION OF EPOC-AD PROGRAMMATIC STRATEGY AND EPOC-AD TRIAL**
  - Comparable to work package 1

- **Work Package 3: EPOC-AD – OPERATIONAL WORKSTREAM**
  - Access to and coordination of on-going natural history studies and patient networks to develop the EPOC registry.
  - Study instruments, biomarkers, imaging, data.
  - CRO activities.

- **Work Package 4: STRATEGIC CLINICAL TRIAL GUIDANCE AND ETHICS**
  - All key expertise areas necessary for the implementation of the work package activities.

- **Work Package 5: GOVERNANCE STRUCTURE AND PROJECT MANAGEMENT**
  - Project management.

- **Work Package 6: - COMMUNICATION AND DISSEMINATION ACTIVITIES**
  - Scientific and media communications expertise.
  - Ethical expertise.
  - Outreach to patients and other key stakeholders.
  - Legal and IP expertise.

- **Work Package 7: - BUSINESS MODEL**
  - Expertise in setting up public-private partnerships

Expected (in kind) contributions of EFPIA members

- **Work Package 1: GOVERNANCE TO ADDRESS THE SCIENTIFIC CHALLENGES**
  - Epidemiological expertise with experience in setting up and maintaining patient registries and natural history methodology studies.
  - Clinical expertise in AD trials.
  - In house data and know-how on AD, including pre-clinical data and assets, and on-going longitudinal natural history/cohort studies
  - Statistical expertise in adaptive trial methodology.
- **Work Package 2: ELABORATION OF EPOC-AD PROGRAMMATIC STRATEGY AND EPOC-AD TRIAL**
  - Comparable to work package 1
- **Work Package 3: EPOC-AD – OPERATIONAL WORKSTREAM**
  - Project management, Clinical operations, Data Management, Statistics, Pharmacovigilance, Regulatory interactions, CRO
  - Direct financial contribution by the sponsoring EFPIA companies, if required, to supplement the clinical study costs (up to 25%), including CRO subcontracting if any, incurred by public partners eligible for IMI funding ensuring that 100% of these costs will be reimbursed.
- **Work Package 4: STRATEGIC CLINICAL TRIAL GUIDANCE AND ETHICS**
  - Clinical expertise in AD, AD R&D and AD trials, Legal, Regulatory.
- **Work Package 5: GOVERNANCE STRUCTURE AND PROJECT MANAGEMENT**
  - Project management.
- **Work Package 6: - COMMUNICATION AND DISSEMINATION ACTIVITIES**
  - Strategies on PPP collaborations; political engagement; legal and IP expertise; regulatory expertise.
- **Work Package 7: - BUSINESS MODEL**
  - Business Development, Legal, Regulatory.

What's in it for you?

- Academic researchers: Access to
  - Relevant datasets and clinical studies
  - Clinical cohorts of at risk individuals and registries
  - Compounds that can be brought into the POC trial
  - collaboration with industrial experts
- SMEs:
  - reduced costs for compound testing (single or combination)
  - biomarker learnings
- Patients' organisations:
  - Involvement with clinical POC testing
  - reduced exposure of patients to placebo
- Regulatory agencies
  - novel experimental design to prevention trials

Key deliverables of the full project

- Strategy for developing rationale for linking biomarkers, mechanisms of disease, read outs, primary outcome measures and treatment and patient selection.

- Development registry of individuals at risk of developing AD dementia who are interested in clinical trial participation.

- Longitudinal natural history study of at risk individuals that will qualify and validate biomarkers and diagnostics that will be critical to AD prevention, and be the basis for the successful selection and stratification of individuals to be enrolled in the trials.

- Adaptive clinical trial which will enable more compounds to be tested with more uniform cognitive outcomes and biomarker readouts.

- The implementation of a clinical trial process and platform with continuous inclusion of investigational compounds and eventual recommendations as to whether to drop a treatment arm either for safety related concerns or futility or to advance it into a separate confirmatory clinical trial.

Key deliverables of the full project

- Implementation clinical trial process and platform with continuous inclusion of investigational compounds and eventual recommendations as to whether to drop a treatment arm either for safety related concerns or futility or to advance it into a separate confirmatory clinical trial.

- Scope for having several therapeutics that run in parallel, and all targeting the same disease hypothesis.

- A Europe wide investigator network of Good Clinical Practice (GCP)-qualified investigational centers, with all necessary training, test materials, and instrumentation to conduct clinical studies of drugs and diagnostic devices and non-interventional trials in at risk individuals for AD and pre-dementia AD subjects.

- A strategy to insure harmonization and standardization.

- A business plan for sustainability beyond the timeframe of the project.

- A public awareness campaign on Alzheimer's at national and international level.

Questions?

- Contact the **IMI Executive Office**

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    Website: www.imi.europa.eu