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D1.2 Description of Compound Selection criteria and decision tree for Proof of Concept trial

WP1 – Scientific Challenges

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DEFINITIONS

- Partners of the EPAD Consortium are referred to herein according to the following codes:
  - **Janssen**. Janssen Pharmaceutica NV (Belgium)
  - **UEDIN**. The University of Edinburgh (United Kingdom)
  - **UOXF.** Masters and Scholars of the University of Oxford (United Kingdom)
  - **BBRC.** BarcelonaBeta Brain Research Center (Spain)
  - **SYNAPSE.** Synapse Research Management Partners S.L (Spain)
  - **KI.** Karolinska Institutet (Sweden)
  - **VU-VUMC.** Stichting VU-VUmc (Netherlands)
  - **UCAM.** Masters and Scholars of the University of Cambridge (United Kingdom)
  - **MRC.** Medical Research Council (United Kingdom)
  - **BERRY.** Berry Consultants LLP (United Kingdom)
  - **UNIGE.** Université de Genève (Switzerland)
  - **RUMC.** Stichting Katholieke Universiteit (Netherlands)
  - **CU.** Cardiff University (United Kingdom)
  - **CHUT.** Centre Hospitalier Universitaire de Toulouse (France)
  - **QUINTILES.** Quintiles, Ltd (United Kingdom)
  - **AE.** Alzheimer Europe (Luxemburg)
  - **EMC.** Erasmus Universitair Medisch Centrum Rotterdam (Netherlands)
  - **APHP.** Hôpital de la Salpêtrière (France)
  - **INSERM.** Institut National de la Santé et de la Recherche Médicale (France)
  - **ULEIC.** University of Leicester (United Kingdom)
  - **IXICO.** IXICO Technologies Ltd (United Kingdom)
  - **ARACLON.** Araclon Biotech S.L (Spain)
  - **FRAUNHOFER.** Fraunhofer-Gesellschaft zur Förderung der angewandten Forschung e.V. (Germany)
  - **Eisai.** Eisai Inc (United States)
  - **SARD.** Sanofi-Aventis Recherche & Développement (France)
  - **NOV.** Novartis Pharma AG (Switzerland)
  - **BI.** Boehriger Ingelheim International GmbH (Germany)
  - **Eli Lilly.** Eli Lilly and Company Ltd (United Kingdom)
  - **HLU.** H. Lundbeck A/S (Denmark)
  - **Takeda EU.** Takeda Development Centre Europe Ltd (United Kingdom)
  - **AC Immune.** AC Immune SA (Switzerland)
  - **Biogen**. Biogen Idec, Inc (United States)
  - **Amgen.** Amgen NV (Belgium)
  - **Pfizer.** Pfizer Limited (United Kingdom)
  - **UCB.** UCB Biopharma SPRL (Belgium)

- **Grant Agreement.** The agreement signed between the beneficiaries and the IMI JU for the undertaking of the EPAD project (115736).
- **Project.** The sum of all activities carried out in the framework of the Grant Agreement.
- **Work plan.** Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in Annex I to the Grant Agreement.
- **Consortium.** The EPAD Consortium, comprising the above-mentioned legal entities.
- **Project Agreement.** Agreement concluded amongst EPAD participants for the implementation of the Grant Agreement. Such an agreement shall not affect the parties' obligations to the Community and/or to one another arising from the Grant Agreement.

ABBREVIATIONS

Abbreviations used throughout the document are listed in the table below.

- **CCSC**. Clinical Candidate Selection Committee
- **CDG,** Clinical Development Group
- **CMC**. Chemistry, Manufacturing, and Controls
- **CSC**. Candidate Selection Criteria committee
- **EFPIA**. European Federation of Pharmaceutical Industries and Associations
- **LCS**. Longitudinal Cohort Study
- **PD**. Pharmacodynamics
- **PK**. Pharmacokinetics
- **PoC**. Proof of Concept
- **SAG(s)**. Scientific Advisory Group(s)
- **VP**. Virtual Pipeline Committee
- **WP***x*. Work Package *number* (ex: WP1, WP2, etc.)

EXECUTIVE SUMMARY

The purpose of this document is to present deliverable 1.2 (D1.2)—"Compound Selection Criteria and Decision Tree for the Proof of Concept Trial"— developed by the Clinical Candidate Selection Committee, an independent work group within work package 1 (WP1). The selection criteria and the decision tree will establish a process for selecting potential mechanisms and compounds for use in the Proof of Concept (PoC) trial, which will utilize the evaluative measures established in deliverable 1.1.

This document is divided into three sections:

1. The first section provides the necessary background on WP1 and the CCSC, including structure, composition, and primary outcomes.

2. Section two details the criteria used for selecting clinical compounds for use in the Proof of Concept trials (PoC).

3. The final section summarizes the procedures for nominating and selecting compounds for study in the PoC (the decision tree).

References and supporting documentation are listed in the appendices.

1. Introduction

The Innovative Medicines Initiative (IMI) European Prevention of Alzheimer's Dementia (EPAD) project includes a secondary prevention adaptive trial aimed at evaluating potential "disease-modifying" drugs in Alzheimer's disease. Greater detail on the background of EPAD can be found in the first deliverable of work package one (WP1),[1] but briefly, the EPAD project consists of three platforms: 1) EPAD Registry, 2) EPAD Longitudinal Cohort Study (LCS), and 3) EPAD Proof of Concept (PoC) Trial.

Eight interrelated work packages (WPs) were formed in order to create the EPAD platforms. The EPAD delivery cluster, a core group of WPs (WPs 1 through 4 with input from WP8), is leading the development of the EPAD platforms. Within the delivery cluster, WP1 is tasked with providing scientific input for the development of the selection criteria and the protocol for data collection. WP1 is composed of three co-leads (Andrew Satlin, Eisai Inc.; Gary Romano, Janssen; Simon Lovestone, University of Oxford), project management support (David Ruvolo, University of Oxford; Ami Saver, Accenture; WP5), five Scientific Advisory Groups (SAGs), and the Clinical Candidate Selection Committee (CCSC, lead: Andrew Satlin, Eisai Inc.; Project Management: Ami Saver, Accenture). The five WP1 SAGs are the Clinical and Cognitive Outcomes (CCO-SAG, lead: Karen Ritchie, Institut National de la Santé et de la Recherche Médicale), Epidemiology (lead: Carol Brayne, University of Cambridge), Fluid Biomarkers (lead: Bruno Dubois, Hôpital de Salpêtrière), Genetics (lead: Julie Williams, Cardiff University), and Imaging (lead: Frederik Barkhof, Stichting VU-Vumc). The SAGs each have approximately six expert members chosen by the SAG leads, as well as external advisors and support staff. The primary outcomes and composition of the SAGs can be found in WP1's previous deliverable and WP composition list.[2-3] The purpose of this document is to discuss the structure, composition, and primary outcomes of the Clinical Candidate Selection Committee ("**CCSC**") and its advisory group to which certain tasks of the CCSC can be delegated as prescribed in the Project Agreement ("**CCSC Advisory Group**").

The preliminary work of the CCSC, in its advisory function, has been divided between two focused interrelated subgroups: the Candidate Selection Criteria committee (CSC, objective: responsible for establishing criteria for compound selection) and the Virtual Pipeline committee (VP, objective: ensuring a steady flow of nominated compounds for the PoC), both led by Andrew Satlin (Eisai). CCSC Advisory Group members were recruited by Andrew Satlin to achieve a balanced representation from the European Federation of Pharmaceutical Industries and Associations (EFPIA), the EPAD consortium, and other non-EFPIA/EPAD members. All members have strong academic experience in Alzheimer's disease and drug development. As a whole, the group has expertise in all areas of drug development including preclinical pharmacology, toxicology, clinical pharmacology, clinical trial design, and regulatory requirements.

The actual evaluation and selection of nominated compounds, which comprises the ongoing executive function of the group, will be conducted by the formally constituted CCSC with membership as prescribed in the Project Agreement.

In order to accomplish the objectives outlined in the DoW, the CCSC was constructed on and produced all outputs in accordance with several key principles.

- We will need a mix of compounds that are close to ready for Phase 2 and some that are earlier in development in order to ensure that the first compound in the PoC study will be identified by one year prior to planned study start, to ensure drug availability, and a steady flow of compounds as the project proceeds. The "virtual pipeline" should assure this availability, but at least at first, the compound selection committee should focus on nominees that are closest to being Phase 2-ready. For earlier compounds, the working assumption will be that Phase-2-readiness will be achieved by the time of the foreseen start of that particular EPAD arm. In order to have an optimal overview for planning, companies are encouraged to contact the CCSC as early as possible to discuss a potential compound nomination

- Our limited understanding of AD disease pathology and its relationship to clinical progression argues for a broad scope in compound selection, openness to new ideas, agnosticism with regard to MoA, and an ability to learn from success or failure. For example, if a compound initially believed to have a high likelihood of success fails, but a compound initially believed to have a low likelihood of success succeeds, what do we learn from that? Overall, the CCSC will need a fair amount of humility in rank ordering at this stage of our understanding of the disease. EPAD is a "continuous learning" project and as such the effects of compounds both in and external to the PoC will inform the future evaluation of compounds nominated for the PoC

- A major issue for the CCSC is balancing their role of facilitating the entry of compounds into the EPAD PoC to provide the engine for drug development that EFPIA partners are expecting, against the possible need to judge the relative value of different compounds and prioritizing them according to likelihood of success in case the number of subjects or investigators is limited

- One way to benefit from the field's evolving knowledge, and to make more informed decisions, is to allow the selection process to be dynamic, collegial, and iterative. For example, compounds early in the "virtual pipeline" could receive preliminary assessments that would be shared with the nominating company to help with their development plans, and could then be re-evaluated at defined milestones prior to final selection for the PoC study. The CCSC is not only an evaluation committee; it should also be the first point of interface for outside groups with EPAD, and a facilitator of the candidate nomination process. As such, the CCSC may consider appointing dedicated advisers, who are bound by confidentiality, to help interested companies in the iterative process of preparing the candidacy of their compounds

- There must be as little bias in the review as possible and no appearance of conflict of interest. This is particularly the case if the compounds are rank-ordered. The CCSC process must be open and transparent.

- The CCSC is not a pseudo-regulatory authority, i.e., it will rely on regulatory authorities to ensure that compounds have met regulatory requirements to advance to Phase 2. Instead, its role is more to de-risk the EPAD project by confirming the scientific rationale, safety, and appropriateness of using EPAD to establish PoC for a given compound

- The EPAD Program is not restricted to pharmacological or biological interventions and can accommodate nutraceuticals. The following criteria are to a greater or lesser degree appropriate for such interventions and the CCSC will advise any proponent of a nutraceuticals intervention of the necessary criteria for selection of that intervention

- The EPAD Program is not restricted to interventions brought by the commercial sector. Academic groups are also welcome to introduce compounds/interventions. The CCSC or its appointed advisers will discuss with such academic groups the necessary criteria they would have to satisfy which may be of particular relevance for a repurposed medication. It should be noted though that funding levels for that intervention would be as they are irrespective of the proponent of the intervention.

2. Compound Selection Criteria for Nominating Compounds

The purpose of this section is to present the clinical compound selection criteria that will be used to implement interventions into the PoC. The compound selection criteria were developed through a series of teleconferences and face-to-face meetings from January to August of 2015.

All compounds selected for potential use in the PoC will be evaluated on the following criteria and rated according to the scoring guide outlined in Section 3.

2.1. Scientific Rationale/Target Validation

- Genetic, pathologic, and/or other convincing data indicating a pathologic involvement of the target with the cause or progression of Alzheimer's disease

- Role of the target suggests the potential for a disease-modifying effect of modulating the target

- Convincing evidence from preclinical studies that the drug molecule effectively engages its target and has the appropriate *in vitro* and *in vivo* pharmacological properties in line with the working hypothesis derived from the above

2.2. Pharmacokinetics (PK)

PK properties determined in Phase I studies support further development and the proposed Phase II clinical plan, including:

- Adequate bioavailability
- Distribution
- Clearance - Low-moderate human systemic clearance determined from Phase I study
- Metabolism - No evidence of reactive metabolites
- Drug/Drug Interaction - No clinically significant DDI (inhibition or induction) at expected clinical doses, or any DDI readily manageable in the clinical setting. No evidence of time-dependent inhibition of human CYPs

2.3. Pharmacology Requirements

- Evidence that the drug molecule has the appropriate potency and selectivity for the target over off-target activities (usually >30-fold)
- Evidence of clear PK/PD relationship to predict likely therapeutic human exposure level
- Phase I data demonstrate that target exposure can be reached without dose-limiting adverse effects
- Ideally, Phase I data demonstrates evidence of PD effect and/or target engagement at exposures consistent with preclinical findings and without dose-limiting adverse effects (Note: EPAD can accommodate compounds that lack this evidence from Phase 1, but such compounds would need to demonstrate an effect on an intermediate phenotype in the first stage of the PoC trial before continuing into the full clinical phase.)
- Data supporting the proposed doses to be used in Phase 2 (e.g., preclinical translation, availability of biomarkers for translation), including data to support the possibility of narrowing down to only 1-2 doses for study in the PoC, i.e., degree of confidence in selecting one or two doses

2.4.Safety

- Appropriate preclinical safety studies in 2 species to support proposed Phase II proof-of-concept study for duration, exposure, and therapeutic index
- Safety data from Phase I studies address preclinical toxicity findings and support

further Phase II development

2.5. Develop-ability/CMC Quality Guidelines

- Formulation strategy to support long-term dosing in planned Phase II study is available
- Simple solutions and/or suspensions are preferred over enabling approaches
- Formulation provides adequate in vivo exposure consistent with solution/suspension assessment
- Chemically and physically stable for the intended shelf-life of the product to support the planned Phase II study
- Availability of adequate non-expired drug supply and matching placebo for completion of proposed PoC trial

2.6. Biomarkers

Assays available for use in the PoC

- Target engagement/mechanism of action pharmacodynamic biomarkers for understanding drug effects
- Suitable for both preclinical species and clinical utility (blood, tissue, imaging)
- Patient stratification markers
- Safety biomarkers

2.7. Plan for studying the compound in the PoC

- High level clinical development plan through to PoC is required
- Proposed population for study, selected from the continuum of subjects available in the Longitudinal Cohort Study
- Proposed duration of treatment required to see a clinical effect
- Proposed clinical endpoints (primary and secondary)
- Proposed biomarker and imaging assessments
- Required special safety assessments, beyond safety measures included in the master protocol

- Hypothesized effect size for determining appropriate sample size

2.8. Plans for full development/regulatory issues

- Preliminary plans for full development post-PoC available at least in draft form

- Regulatory filing completed (CTA or IND) and Clinical Documentation available (e.g., Investigator's Brochure, early clinical study results, regulatory feedback and evidence that any regulatory requirements specific to the compound are being addressed or can be addressed in the PoC)

2.9. Additional criteria that can be used/considered for prioritization of candidates

- Degree of innovation, e.g., novelty of target

- Ease/acceptability of mode of administration

- Potential for use in combination with other candidates

- Ideally, it should be possible to randomize a new subject to any of the drugs currently being studied in the PoC. To make this ideal a reality, all drugs would need to be similarly "acceptable" to subjects entering a trial, e.g., in terms of safety, mode of administration, frequency of assessments/visits, etc. A drug that is very different in these respects from others already in the study would pose more challenges and might for that reason be de-prioritized, at least temporarily. In effect, we would like the degree of equipoise regarding the benefit-risk of all compounds in the study to be as closely comparable as possible

- Availability of funding (note: for projects that come from sources other than industry, funding could come from in-licensing by a pharma company or from public or private grants). Consideration should also be given to whether there is potential funding for Phase 3 studies if the candidate is successful in the PoC

3. Nominating and Selecting Compounds for Study in the PoC

The purpose of this section is to present the decision tree which contains all procedures and processes for selecting/nominating compounds for use in the PoC. The decision tree is based on selection criteria developed in the previous section and developed through a series of teleconferences and face-to-face meetings from February to August of 2015.

3.1. CCSC Process Flow

The CCSC developed a method for soliciting, nominating, and selecting compounds for study in the PoC that is outlined below. Supporting documentation mentioned in item one can be found in Annex I:

1. CCSC sends Preliminary Questionnaire and other supporting documents (Value Proposition slides, EPAD-PoC FAQ; Candidate Selection Criteria document and Scoring Guide; CCSC Process Flow; draft LCS and PoC Master Protocol synopses) to all EFPIA companies to solicit interest and questions, first targeting companies that have already indicated an intention to nominate a compound for the PoC; performs competitive intelligence exercise to identify potential compounds from other sources and sends selected potential nominators the Preliminary Questionnaire and other supporting documents

2. CCSC reviews returned questionnaires and notes the potential fit of proposed compounds for the PoC

3. CCSC also reviews unsolicited expressions of interest and sends Preliminary Questionnaire and other supporting documents to other potential nominators

4. CCSC meets with owners of potentially acceptable compounds to address concerns and resolve issues, and provides the Nomination Form as requested

5. CCSC notifies the Clinical Development Group (CDG) of the potential nomination and its probable timing; CDG initiates assessment of feasibility and preliminary planning for development of the amendment/appendix that will support the inclusion of the compound in the PoC, but without adaptation of the LCS recruitment at this time

6. The CCSC members and the compound owner will agree on mutually acceptable confidentiality requirements to enable review by the CCSC members. For the avoidance of doubt, CCSC members shall not provide confidential information about the compound to CCSC advisers or consultants who are not CCSC members without the prior written consent of the compound owner, and, if requested by the compound owner, without having a CDA in place between that compound owner and the CCSC advisers or consultants who are not CCSC members.

7. Based on the above actions, CCSC begins to create the virtual pipeline, using the

Candidate Spreadsheet

8. Compound owners submit formal Nomination Form

9. CCSC conducts preliminary review of Nomination Form to determine whether additional experts are needed for the review; a primary reviewer is assigned and meeting date is set. In case any additional expert is needed, the compound owner shall be informed and needs to provide prior written consent before any compound information is provided to such additional expert(s). The expert(s) shall also be required to enter into the CDA referred to in Clause 6 above if so requested by the compound owner.

10. CCSC Review: CCSC meets, reviews the nomination and all supporting documentation, completes the Evaluation Form, and makes formal decision about inclusion of the nominated compound in the PoC. Three decisions are possible: (1) compound accepted; all required preparation for inclusion in PoC to commence as soon as possible; (2) compound deferred; nominator requested to provide additional information and/or to re-submit at a later date; (3) compound rejected. Accepted compounds enter virtual pipeline and timelines are finalized. CCSC notifies the CDG and adaptations to recruitment to the LCS are made from the virtual register to ensure its replenishment

11. Compound owner drafts appendix with UEDIN as sponsor and all necessary governance documentation (EMA, ethics etc.)

12. Appendix/amendment reviewed per EPAD requirements and approval received

13. PoC Trial commences

ANNEXES

Annex I. Virtual Pipeline FAQ
Annex II. EPAD CCSC Preliminary Questionnaire
Annex III: EPAD PoC Value Proposition Slides
Annex IV. Clinical Candidate Evaluation Criteria Scoring Guide
Annex V: Notes

Annex I. Virtual Pipeline FAQ

1. What is the purpose of EPAD? *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.*

2. What patient populations will be enrolled into the EPAD longitudinal cohort?
    a. Diagnosis – *The Longitudinal Cohort Study (LCS) will include subjects with evidence for AD pathology.*
    b. Severity – *The study population will span the full continuum from no symptoms (i.e., preclinical AD) through the late stages of prodromal AD (or MCI due to AD) but will not include anyone who already meets criteria for a diagnosis of dementia.*
    c. Biological fingerprint – *The imaging modalities and biomarkers that will be used to characterize the LCS population are still under discussion. However, the requirement for AD pathology necessarily entails the use of either PET imaging or CSF or both. It is likely that subsets of the population will have both assessments. The LCS may also include some subjects who have some evidence for AD pathology but who do not meet standardized cut-offs for*

amyloid positivity (i.e., who are in a "gray zone" pathologically) and some control subjects who are amyloid negative.

d. Genetics – *The LCS population will comprise sporadic AD and not dominantly inherited AD. The population selection process may involve some enrichment for ApoE4+ genotype, but the full population will include subjects who are both ApoE4+ and -.*

3. What data will be collected from these subjects?
   a. Cognitive – *A cognitive battery that is appropriate for the full spectrum of cognitive status in the LCS population and that is sensitive to change over time is being developed and will be used to follow LCS subjects at regular intervals. The availability of such longitudinal run-in data for subjects who are eligible for the PoC trial is a key advantage of the EPAD project as it will provide individual data on the rate of decline that can serve as a baseline set of assessments, which will increase the study's power to detect change due to treatment.*
   b. Behavioral – *Assessments of depression, anxiety, and sleep are proposed.*
   c. Functional – *A functional assessment will be included. At this time, the Amsterdam IADL Scale is being considered, and actigraphy may be included.*
   d. Imaging – *PET amyloid imaging and MRI, including fMRI, will be included. Others may be added.*
   e. Tissue – *See above.*
      i. CSF
      ii. Plasma
      iii. DNA

4. EPAD Longitudinal Cohort Study and EPAD PoC logistics
   a. Where are these subjects going to be seen and followed? – *The EPAD project includes approximately 30 Trial Delivery Centers (TDC) that will conduct both the LCS and the PoC trial. These centers are highly experienced and will undergo further training*

for standardization as part of EPAD. Currently the project only includes TDCs in the EU. However, efforts are underway in other regions to establish projects similar in aim and scope to EPAD, e.g., GAP in the US and similar proposed projects elsewhere. It is envisioned that subjects and TDCs in these regions may become collaborators with EPAD. Ideally, a similar LCS, and the same PoC trial, will be conducted globally with participation of these other regional partners.

b. How often will subjects be seen? – *The frequency of follow-up in both the LCS and PoC are under discussion as part of the protocol development process.*

c. How long will they be followed? – *The LCS will continue through the full 5-year duration of the EPAD project. Planning is already underway to sustain the cohort beyond the project duration.*

d. Will their data be available to EPAD members? - *All LCS data will be available to all EPAD members in accordance with the access rights provided for in the EPAD Project Agreement.*

5. EPAD PoC study design
   a. What are the core elements of the EPAD PoC study design? – *Key features of the PoC study design are use of a cognitive measure as the primary endpoint; frequent interim analyses for success and futility; advancement of compounds that achieve an effect on an intermediate phenotype or biomarker of target engagement to the clinical stage of the study (note: compounds that have already demonstrated target engagement may bypass this step); Bayesian statistical models used to adapt on the cognitive measure to achieve faster randomization to doses/drugs that appear more effective overall or in specific subpopulations; efficient use of the accruing data, e.g., by utilizing all assessments within a longitudinal model; randomization to drug or placebo for each intervention, with analysis using combined data from all placebo subjects to increase the power of the analyses.*

b. What elements are fixed? – *There will be a set of efficacy and safety measures that will be assessed in all subjects. Additional measures that are specific to the drugs being studied can be included as needed.*

c. What elements are adaptive? – *The key adaptive features will be adaptive randomization of subjects and the ability to discontinue a drug treatment for futility or evidence for early success in the PoC, i.e., efficacy data indicating readiness for Phase 3. Adaptive randomization could be used to preferentially assign subjects to doses of a drug that appear more efficacious at an interim analysis (IA). It is also possible that subpopulations of subjects, defined by clinical, biomarker, or genetic criteria, could be preferentially randomized to a specific drug based on evidence for greater efficacy of that drug in that subpopulation at an IA. Other adaptations could be considered if warranted by the needs of a drug or drug owner.*

d. What is the analysis plan for these data? *The primary analyses will utilize Bayesian statistics. This approach is more powerful for determining the probability of success of a given drug at multiple interim analyses and therefore will lead to faster decision-making.*

e. How will amendments be handled? – *Essentially, the addition of each new drug to the PoC entails an appendix in which the specific treatment parameters and assessments are described. Such appendices or amendments will be developed jointly by the EPAD Clinical Development Group (CDG - responsible for overall study design) and the compound owner.*

f. How flexible is the study design? Will individual compound owners be able to specify trial design features for their compound? – *The efficiency of the EPAD PoC trial, and therefore to some degree its value proposition to any participating compound owner, is enhanced to the extent that standardized use of populations, endpoints, and analyses are shared among all compounds being studied. However, compounds that for any reason require a more individualized approach can also be accommodated within the*

EPAD PoC. Discussions about these approaches will begin at an early stage of the candidate selection process, so that compound owners and the CCSC can work together to address any issues. There is no problem at all with including specialized biomarker, exploratory clinical endpoints, or required safety assessments specific to the compound being nominated.

6. Study intervention
    a. What therapies will be considered? – *A Clinical Candidate Selection Committee (CCSC) will evaluate all nominated compounds or other interventions. The process is agnostic to mechanism. All interventions that have scientific support for potential efficacy in the prevention of AD dementia or delay in progression of symptoms in the full secondary prevention LCS cohort or any subset of it, and that have adequate preclinical and clinical safety to support advancement to Phase 2, are eligible. Novel small molecules, repurposed molecules, biologics, vaccines, nutraceuticals, and combinations of any of the above can be considered.*
    b. What data are required to have a therapy considered? – *The same data that would be used to explain to regulators, IRBs, investigators, and potential subjects the rationale for testing, and evidence for preliminary safety, of any compound proposed for study in a Phase 2 trial would be required also for inclusion in the EPAD PoC. EPAD is intended to facilitate the determination of PoC for compounds in development for AD; essentially, any compound that would be considered ready for such testing should already have the data needed to be eligible for inclusion.*
    c. How will a therapy be selected for entry into the study and by whom? – *As noted, the CCSC will review nominations and select compounds. The criteria will be standard ones for advancement to Phase 2, without additional requirements to meet any hypothesis regarding AD etiology or pathogenesis. The CCSC will be comprised of experts in AD and in drug development. In the event*

that compounds must be prioritized, the criteria and scoring for such prioritization will be clear, predefined, and transparent. The CCSC and compound owners will work closely, beginning long before the actual initiation of the study, to ensure that the timing of inclusion of the drug will work for the compound owner and that EPAD will be ready to add that compound to the study on the expected timeline.

d. How will bias or conflict of interest be controlled for in the selection of therapies? – *Members of the CCSC will be required to sign confidentiality agreements before reviewing nominations. The CCSC will not include anyone with potential conflicts of interest regarding the inclusion of the compound being evaluated.*

e. What about potential synergistic combinations? – *Testing combinations is a specific goal of EPAD and it is expected that combinations of therapies will be proposed for inclusion. The same criteria will be used for selecting combinations as for selecting single therapies.*

f. How will proprietary information be protected? – *The EPAD Project Agreement includes confidentiality provisions that are also applicable to employees of EPAD members. However, if requested by the compound owner, all members of the CCSC will sign confidentiality agreements before reviewing confidential information from that EPAD member. Confidential information will be submitted and maintained using secure processes with limited access. Submission of a full nomination will only occur after informal discussion with the CCSC to ensure that a compound has all data sufficient for evaluation.*

g. How will safety information be handled so that the owner of the therapy remains compliant? – *A single academic entity (University of Edinburgh) will be the sponsor of the EPAD PoC trial and will be responsible for all safety reporting. The owner of the drug will also receive all safety data that might be associated with the use of that drug.*

7. Study data
    - ***a.*** Who owns the study data? - *All data specific to a drug in the PoC will be owned by the owner of that drug, with exceptions for data specific to proprietary biomarkers used in the PoC.*
    - *b.* Who will have access to the data owned by the compound owner? *In accordance with the IMI principles, each EPAD member and any third party shall have the right to request access to all PoC data owned by the compound owner. The restrictions on such access rights depend on the type of data and whether an EPAD member or third party requests them. EPAD members can request access rights for research use after finalization of the relevant PoC trial report insofar as they grant the compound owner a license on the results they generate when exercising such access rights. Third parties can request access rights for research use from two years after completion of the EPAD project (or the date on which the relevant PoC trial report has been finalized, if later). The terms of third party access rights are to be negotiated between the compound owner and the requesting third party and may include further delays, financial terms, and a license grant back on results of the access rights.*
    - *c.* What are the reporting obligations regarding clinical trial data? – *The reporting requirements as determined by local regulations are the same as for any clinical trial.*
    - *d.* How long will the data be archived? – *The requirements for any clinical trial will be adhered to.*
    - *e.* How will privacy requirements be handled? – *See above.*

8. Study logistics
    - *a.* How many subjects are likely to be available to the study at a given time? – *A key advantage of the EPAD PoC is the trial-ready availability of subjects from the LCS for randomization. The LCS is expected to be following 6,000 subjects at any given time and will be replenished as subjects are recruited into the PoC.*

b. What is the expected enrollment rate from the cohort into the study? - *The randomization rate is only limited by the resources of the TDCs (which are designed to be adequate such that this is not rate-limiting) and can be set to be most efficient for the adaptation process within the PoC trial.*

c. How are the different components of the EPAD project funded?– *The IMI grant award includes direct funding from IMI and additional funding in-kind and in cash contributions from EFPIA participants. The information is available and transparent. This funding fully covers the set-up and conduct of the LCS, qualification and training of the TDCs, preparation of the PoC protocol, contracting with all PoC study sites and vendors, and regulatory submission of the PoC master protocol. Owners of compounds included in the PoC are only responsible for the direct costs of studying their compound, including a portion of the costs of the placebo group.*

d. Who is accountable for auditing/quality control of the study? – *As in any clinical trial, this accountability lies with the sponsor. There will be a single academic sponsor (University of Edinburgh).*

e. Who is accountable for the medical governance of the study? – *See above.*

f. Who is accountable for analyzing study data? – *Again, all accountability lies with the sponsor. The project will contract with an independent external vendor for data management and data analysis. The Bayesian analyses will be run using predefined algorithms that will direct the adaptations. An independent statistical group will monitor the interim analyses to ensure that they are being conducted in accordance with all requirements of the protocol.*

g. How will unblinding of the results occur? *The results will be blinded to everyone until the point that any given drug achieves early success or futility. It is the intention that, once a signal for early success or futility for any given compound is detected, the full*

data, including placebo data, will be made available to the owner of that compound.

h. Who is accountable for site training/coordination? – *The sponsor is accountable and will select a vendor to perform these tasks.*

i. How is EPAD funded and for how long? – *The EPAD project is funded by EFPIA companies with in-kind and cash contributions, and by matching funds from IMI. The total duration of the project is 5 years, but a key project goal is to achieve sustainability beyond this point, assuming the project is viewed as attaining its goals. Regarding the funding of any individual drug component of the PoC trial, the owner of that drug will be responsible for direct trial costs, including drug supply, investigator fees, IVRS, monitoring costs, etc. Many of these costs are expected to be significantly lower than those of a comparable trial conducted independently because of the available infrastructure, trained investigative sites, and trial-ready subjects available through EPAD.*

j. How will investigational compounds be handled? – *Similarly to the processes for any clinical trial.*

9. Regulatory aspects
    a. Has the EPAD study design been shared with regulators? – *Informal discussions have already taken place. A strategy has been decided for obtaining scientific advice from CHMP for both the LCS and PoC protocols.*
    b. What have regulators had to say about this cohort/study plan?
        i. EMA – *EMA is enthusiastic about the potential advantages of the EPAD project and has indicated an interest in reviewing key aspects with regulatory implications as early as possible.*
        ii. FDA – *FDA has indicated an interest in being invited to EPAD meetings with EMA. The GAP project, a potential sister project to EPAD, has already had FDA input into its design.*

iii. Others? – *Discussions with other regulatory authorities have not yet occurred.*

c. Could data obtained from the EPAD study be used to support a registration filing? –*This is our intention and will be a key question for our discussions with regulators. The trial will be rigorously conducted, meeting all regulations and data compliance standards. We will discuss the proposed clinical endpoints and their acceptability for use in a pivotal trial based on their ability to demonstrate proof-of-concept.*

d. Will data collected in this study be of sufficient quality to be accepted by regulators? – *We believe so and will discuss details with regulators.*

e. Could the owner of a compound roll subjects in their treatment arm seamlessly into a Phase 3 trial after a signal of early success in the Poc? – *Theoretically, this may be possible. There would be many hurdles, including how to manage placebo subjects, statistical plans, and transfer of sponsorship. These questions will also be addressed with regulatory authorities.*

10. Value Proposition

The EPAD Value Proposition slide deck presents the EPAD PoC trial as a "better, faster, cheaper" way to get to Phase 3. Better, faster, cheaper than what? Can you quantify any of this?

"Better" *– the EPAD PoC will provide robust clinical data to establish the potential efficacy of a new compound, and to improve dose selection, choice of primary endpoint, and possibly definition of the optimal target population for Phase 3. These outcomes have always been expected from traditional Phase 2 trials, but such trials have been rare in the recent history of AD drug development because of their cost and duration. The EPAD PoC makes the conduct of such a trial feasible by reducing cost and duration through the use of novel, more sensitive cognitive endpoints and the use of a Bayesian adaptive design that maximizes the efficiency of data analysis and permits decision-making based on the earliest possible signals of success or failure (i.e., at frequent interim analyses). The trial provides extensive*

data for designing Phase 3, leading to greater likelihood of overall success.

***"Faster"** – In addition to decision-making based on early signals of success or failure from frequent interim analyses, which will permit the initiation of Phase 3 trials earlier, participation in the EPAD PoC also accelerates timelines by speeding study initiation and recruitment. Trial initiation is accelerated because the master trial protocol, TDC contracts, vendor contracts, database structure, and statistical analysis plans are all ready for use. While individual compound owner companies can work on some of these aspects upfront and at risk when conducting studies independently, it is expected that participation in the EPAD PoC will reduce the white space between Phase 1 and 2 by at least several months. Ease of subject recruitment is one of the greatest benefits of EPAD PoC participation. Assuming a sample size of 500 subjects, a sponsor company might typically consider that 100 sites might be needed, with each expected to enroll about 0.2 subjects/month (given the difficulty of identifying preclinical or prodromal AD subjects), resulting in a recruitment period of about 2 years. In EPAD, given that subjects will be recruited from the LCS, which will be following 6,000 well-characterized subjects who have already expressed an interest in participating in a clinical trial, it is expected that the TDCs will be able to enroll about 1 subject/week, or 4/month. With 30 TDCs, and assuming that 3 compounds are being studied at any given time (i.e., that only 1/3 of new subjects are randomized to any given treatment or its placebo), about 500 subjects per compound could be randomized in 1 year , saving 1 year in recruitment time. Finally, recruitment in a traditional trial ramps up as sites are slowly initiated; in the EPAD PoC, all sites are ready to enroll at their maximal rate from Day 1.*

***"Cheaper"** – In addition to recruitment being faster, it will be cheaper because of a greatly reduced screen failure rate due to the availability of well-characterized subjects in the LCS. It is expected that a typical rate of screen failure of 75% for prodromal AD trials could be reduced to 25%. Fixed costs of the PoC trial, including protocol development, SAP development, contracting, site feasibility, etc. will be shared among the owners of the drugs being studied, which are expected to be about 3 at any given time. The costs of studying the placebo subjects are also shared among all drugs being studied. Monitoring costs will be reduced because of the use of fewer trial sites*

than might be required without a trial-ready cohort and because they will be certified as experienced and trained prior to trial initiation. Overall project management costs will be reduced because of the shorter duration of the trial than a traditional trial.

11. Once my company has committed a compound for inclusion in the EPAD PoC, can I be sure that there will be an open slot that fits with my project timelines? – *Yes. The availability of the EPAD subjects from the LCS and the infrastructure in the PoC assures predictability in planning for compound inclusion. The process for compound nomination to the CCSC begins long before FPI, on a timeline that mirrors the way that pharmaceutical companies plan their project development. This process is iterative and recognizes that timelines sometimes require adjustment as a drug proceeds through early development studies. The CCSC will work with potential compound nominators to assure optimal predictability in the timing of PoC initiation for their compound. A key function of the CCSC is to facilitate compound inclusion in the PoC and to de-risk the selection process as it proceeds. Please see the CCSC Candidate Selection Criteria and Process Flow documents for more details.*

12. So our compound will not be de-prioritized if there is another compound with the same mechanism from another company that has already been approved by the CCSC? – *That is correct. The EPAD project is designed as an engine for drug development. All suitable compounds can be studied, and the EPAD LCS has adequate flexibility to manage the LCS and TDCs to ensure that compounds that are ready can enter the PoC.*

13. We are conducting a global development. Why should we conduct a PoC study solely in the EU? – *A rigorous and large Phase 2 PoC trial conducted solely in one major geographic region should be acceptable to progress to a global Phase 3 development targeting registration in all major regions. Despite the limited geography, the trial will not be limited in size and in fact will be completed more quickly than a typical Phase 2 trial of the same size conducted in several regions. That said, we are hopeful that the GAP project in the US and similar projects in other*

regions will align with EPAD to provide a larger, globally integrated platform in the near future.

Annex II: EPAD CCSC Preliminary Questionnaire

Note: This questionnaire is a non-binding expression of interest to the EPAD Clinical Candidate Selection Committee (CCSC) and a preliminary presentation of information about a potential candidate compound to facilitate discussion with the CCSC prior to submission of the formal Nomination Form. It has been designed to elicit non-confidential information to expedite the process. If you prefer a signed Confidential Data Agreement (CDA) prior to responding to this questionnaire, please let us know and one of the CCSC members will contact you. Should you choose to proceed to a formal submission of your compound as a candidate, a CDA will be signed at the time of submitting the formal Nomination Form to ensure the confidential handling of the required documentation (e.g., Investigator's Brochure, regulatory correspondence, preclinical and clinical study reports, etc.).

A. Is there a general interest in studying one of your compounds for the secondary prevention of AD in the EPAD PoC trial? YES/NO

B. If yes, by when do you anticipate your compound will be ready to enter the EPAD PoC trial from a current perspective (indicate year and quarter, e.g., Q2 2017):

Additional information (as mentioned, this questionnaire has been designed to elicit non-confidential information to expedite the process. If you prefer a signed CDA prior to responding to this questionnaire, please let us know and one of the CCSC members will contact you):

1. Presumed target of the compound (e.g., amyloid, tau, inflammation, neurotransmitter, mitochondria, other):

2. Is there human evidence for target engagement (yes/no)?

3. Nature of intervention (e.g., small molecule, antibody, vaccine, nutraceutical, other, etc.):

4. Has suitability for advancement into Phase 2 been discussed with any regulatory authorities (yes/no)? If so, have they concurred with readiness for Phase 2 (yes/no)?

5. The EPAD secondary prevention population includes subjects ranging from at-risk of AD with evidence for AD pathology but without clinical symptoms (i.e., "preclinical" AD) through prodromal AD (i.e., mild cognitive impairment due to AD), but without evidence for dementia. Is the population proposed for study with your compound within this scope and, if so, would it encompass the entire population or a subgroup? If a subgroup, can you provide the nature of the subgroup?

6. Are there available biomarkers for testing target engagement, or for detecting downstream pharmacodynamic effects of the compound (yes/no)?

7. Will any special safety assessments (e.g., imaging other than neuroimaging, invasive procedures, etc.) be required in Phase 2 (Note: it is not necessary to specify the assessment at this time)?

8. Can you confirm that you will be able to provide adequate drug supply and matching placebo?

9. Can you confirm that you are willing to provide funding for your portion of the PoC?

10. Please list any questions or concerns you might have about nominating your compound or about studying it in the EPAD PoC:

Annex III: EPAD PoC Value Proposition Slides (*in case of contradiction between the slides and the other parts of this document, the other parts of this document will prevail).

1

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

2

EPAD

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.

www.ep-ad.org

3

EPAD

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*

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EPAD

The EPAD Solution

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*

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EPAD

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

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EPAD

Bayesian Adaptive Design Advantages

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.

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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

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"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

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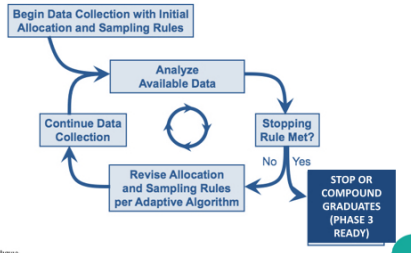
9

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

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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

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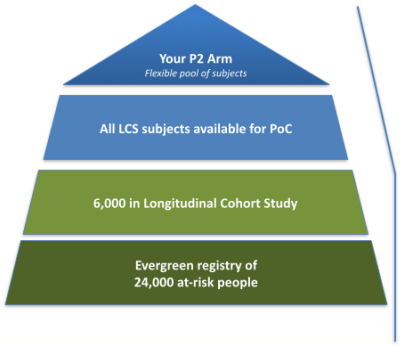
Subject Recruitment: How It Works



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

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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

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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

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Trial Efficiencies: A Quicker Outcome Lowers Costs

QUINTILES TO REVIEW

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	1+ subjects/site/ month	< 20% SFR	PM and medic time for less than 6 months	Already in place
POTENTIAL EPAD COST BENEFIT	4-5x faster	~50%+ SFR benefit	6 months trial management cost savings	Time and money

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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

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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

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4. Other Benefits

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

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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.

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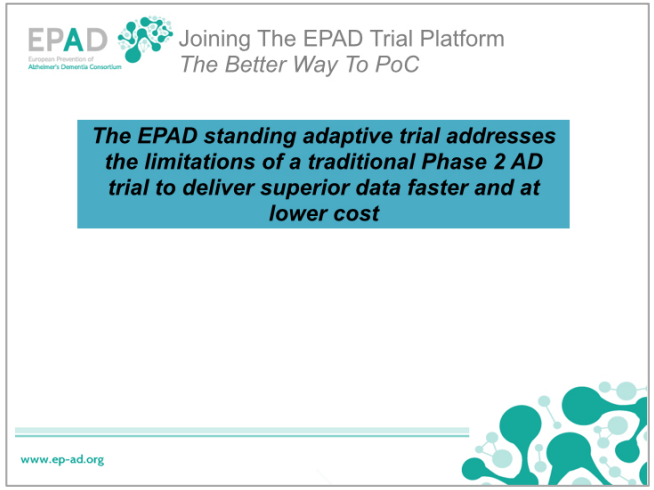

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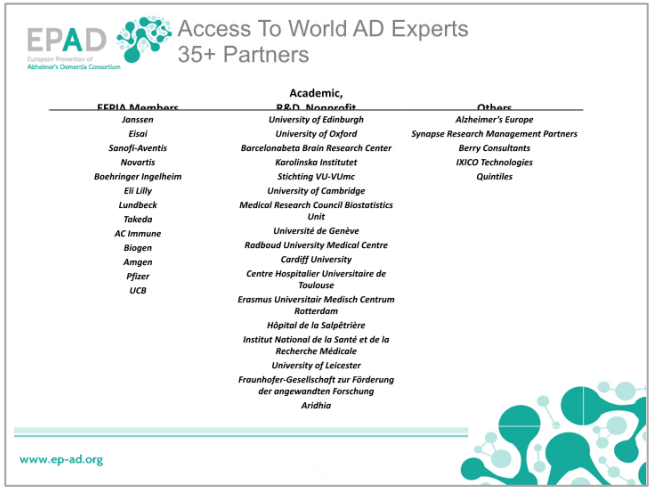

Annex IV. Clinical Candidate Evaluation Criteria Scoring Guide

Criterion	Data Evaluated	High (H) Rating	Medium (M) Rating	Low (L) Rating	Rating	Rationale for Rating
Scientific Rationale / Target Validation	Human disease genetic linkage Cellular models Animal models Human neuropathology Relevant bioassays Tool compounds	Genetic linkage to AD Compelling scientific rationale Highly validated, consistent across multiple preclinical models Clinical evidence for other agents in the same class, e.g., BACE-inhibitor	Somewhat validated; some convergent evidence across models	Validated in a single model; weak or conflicting evidence		
Pharmacokinetics	Bioavailability Distribution Metabolism Drug/Drug Interaction CNS Exposure	Established, predictable PK profile Clinically viable dosing regimen Known, adequate exposure in relevant compartment (e.g. CNS exposure as measured in CSF) Established clearance mechanism No reactive metabolites Low DDI	Manageable PK issues (e.g., non-linear, concentration-dependent clearance mechanisms) Uncertainty in PK relationships or dose prediction which can be managed in Phase 2 Metabolites of minimal clinical importance Manageable DDI, e.g., does not require limitations on use of commonly prescribed co-medications, although dosing may be affected	PK limitations (high clearance/metabolism, challenging dosing regimen, metabolites) DDI of concern, e.g., requires exclusion of co-medications commonly used in the target population		

Criterion	Data Evaluated	High (H) Rating	Medium (M) Rating	Low (L) Rating	Rating	Rationale for Rating
Pharmacology/ Pharmacodynamics	In vitro assays Animal dosing Phase 1 or 2 Dose/PK/PD relationships Target selectivity (related targets, "downstream" targets, off-targets, safety)	Strong PD effect: potent, concentration dependent, and reproducible PD effect strongly linked to scientific rationale/target validation Evidence for downstream effect Strong dose justification Clear rationale for limiting PoC study to 1-2 doses No target selectivity issues	Moderate to good PD effect: PD effect identified, but unclear linkage to scientific rationale/target validation No downstream effect Identified May need to study >2 doses in PoC Manageable selectivity issues	Weak or marginal to suboptimal PD effects Limited linkage of PD effect to scientific rationale/target validation No clear dose rationale Selectivity issues of concern		

Criterion	Data Evaluated	High (H) Rating	Medium (M) Rating	Low (L) Rating	Rating	Rationale for Rating
Safety	In vitro assays Animal toxicology Phase 1 and 2 Liver CV Immunogenicity Etc	Consistent, predictable safety profile No significant safety concerns in Phase 1 or Phase 2a (especially with higher exposures, larger number of subjects exposed, subjects with AD pathology v. HV, and longer duration of treatment in Phase 1/2a) High margins for safety Assays available for specific safety issues (e.g., metabolites, immunogenicity) General safety measures as in core protocol are sufficient	Well established safety profile Manageable safety concerns in Phase 1 or Phase 2a (especially with higher exposures, larger number of subjects exposed, subjects with AD pathology v. HV, and longer duration of treatment), or no significant safety concerns with smaller number of subjects exposed or shorter duration of treatment in Phase 1/2a Good safety margins Manageable safety issues with risk-management plan Assays under development for safety issues Requires additional safety testing that would only be conducted in this EPAD-arm but that can easily be managed operationally at the sites (e.g., more frequent visits, a higher ECG frequency)	Complex safety profile. Safety concerns with small numbers of subjects exposed or short duration of treatment in Phase 1/2a or no data on subjects with AD pathology; may be manageable Safety margins may limit dose range Complicated risk-management None or complex assays for safety issues Requires additional specific safety testing that would only be conducted in this EPAD-arm and that increases operational burden and/or cost (e.g., unusual procedure, or requiring referral to another discipline, etc).		

Criterion	Data Evaluated	High (H) Rating	Medium (M) Rating	Low (L) Rating	Rating	Rationale for Rating
CMC	Formulation strategy for Phase 2 Stability, solubility, absorption, bioavailability Drug supply	No significant CMC issues (comparability with Phase 1/2a material; stability at expected storage conditions; well-defined formulation or delivery system; available matching placebo) Adequate drug supply for EPAD clinical trial No issues with packaging, storage, or distribution	Manageable CMC issues (stability supports short or specialized storage conditions; manufacturing changes with nonsignificant differences in comparability from Phase 1/2a material; less common formulation or delivery system; placebo with low risk of unblinding) Adequate drug supply for EPAD clinical trial Manageable issues with packaging, storage, or distribution	CMC issues of concern (stability may only support very specialized storage conditions; significant process changes or differences in comparability from Phase 1/2a material; challenging formulation or delivery system; risk of unblinding vs placebo (e.g., colored IV infusion) Potential supply limitations Logistically difficult issues with packaging, storage, or distribution		
Biomarkers - Patient selection	Population-based biomarker	No patient selection/stratification required (i.e., full LCS population can be studied); OR, evidence-based opportunity for patient selection/stratification/personalized medicine approach, e.g., ApoE4+ only, with established biomarker available	Drug target and/or mechanism of action suggests patient selection/stratification required for efficacy or safety but biomarker available	Drug target and/or mechanism of action suggests patient selection/stratification required for efficacy or safety but no biomarker available		

Criterion	Data Evaluated	High (H) Rating	Medium (M) Rating	Low (L) Rating	Rating	Rationale for Rating
Plan for studying the compound in the PoC	Proposed population for study, selected from the continuum of subjects available in the Longitudinal Cohort Study Proposed duration of treatment required to see a clinical effect Proposed clinical endpoints (primary, selected from among those already included in the master protocol, and secondary) Proposed biomarker and imaging assessments Required special safety assessments, beyond safety measures included in the master protocol Hypothesized effect size for determining appropriate sample size	All of the flexible PoC study design features have strong scientific rationale and will contribute to the likelihood of success of the compound The proposed special assessments are feasible and practical and will not unduly add to the complexity of the study or the burden to investigators and participants	Some of the flexible PoC study design features have strong scientific rationale; others are largely based on desired characteristics of the treatment or on standards used in other AD development projects The proposed special assessments add complexity or burden but can be accommodated within the master protocol	Few of the flexible PoC study design features have strong scientific rationale and are largely based on desired characteristics of the treatment or on standards used in other AD development projects The proposed special assessments add considerable complexity or burden and do not permit the use of pooled placebo subjects		
Intent to pursue Clinical Development Plan after PoC	Criteria for continued development (positive PoC) Phase 3 development strategy	Well defined, objective criteria for a positive PoC Feasible Phase 3 development program supporting registration, with established regulatory pathway	Objective criteria for positive PoC Phase 3 program under development Requires novel study designs or features that will require regulatory acceptance	Criteria for positive PoC broad or poorly defined Limited Phase 3 planning or history of negative feedback from regulatory authorities		

Criterion	Data Evaluated	High (H) Rating	Medium (M) Rating	Low (L) Rating	Rating	Rationale for Rating
Regulatory status and documentation	IND Investigator brochure Regulatory correspondence	No regulatory or documentation issues	Manageable regulatory concerns	Significant regulatory concerns		
Other	Innovation Potential for combination Ease/acceptability of mode of administration	Ratings are not suggested for these topics. For innovation, factors to be considered could be the novelty of the target or the novelty of the approach to targeting a well-validated pathology. For combinations, factors to be considered could be the rationale supporting a synergistic effect, or the availability of biomarker or safety data supporting the combination, or feasibility based on the status of the proposed components, e.g., combining a novel agent with a re-purposed (i.e., already licensed) one. For mode of administration, consider oral v. sc v. iv; similarity to other agents already in PoC				
Availability of funding		Includes acceptance of EPAD platform elements, e.g., Edinburgh as sponsor, single CRO, existing cross platform DSMB, EPAD PoC funding model, etc.				
SUMMARY EVALUATION						

Annex V. Notes

[1] WP1 Deliverable 1.1: Evaluation of pre-clinical and prodromal diagnostic criteria, risk spectrum and inclusion criteria for Register and Cohort (https://epadpm.teamwork.com/files/1885537)

[2] EPAD Description of Work: https://epadpm.teamwork.com/files/1121596?v=1 (p24 – 31)

[3] EPAD WP1 contact list (.xlsx): https://epadpm.teamwork.com/files/1798928