Webinar | IMI2 - Call 7
‘Dry age-related macular degeneration: development of novel clinical endpoints for clinical trials with a regulatory and patient access intention’

Friedrich Asmus

IMI webinar • 19.01.2016

Project Background

- Age-related macular degeneration (AMD)
  - chronic progressive disease
  - among the leading causes of legal blindness worldwide
  - comprises early, intermediate and late AMD.
    - The term „Dry AMD“ is used for intermediate and late/ advanced AMD but not for neovascular (wet) AMD.
  - Impairment of visual function starts in early AMD and progresses to late AMD with vision-threatening complications like neovascularizations or irreversible “Geographic” Atrophy (GA) of the retina.
- GA affects up to 10% of all AMD patients;
  UK prevalence: 276’000 patients, expected to rise to ~400,000 patients by 2020.

imi innovative medicines initiative

Specific Challenges of the Project - I

- Currently effective treatments are only available for neovascular AMD. No therapeutic options exist to stop or delay the
  - transition of intermediate AMD to GA and
  - progression of GA.
- Prerequisite for successful drug development in both disease states are novel, appropriate and validated clinical endpoints
  - with high sensitivity and specificity
  - meaningful to patients (patient relevance!)
  - measuring visual dysfunction beyond best-corrected visual acuity (BCVA).

Specific Challenges of the Project - II

- BCVA only captures central visual function and may stay normal even in advanced GA stages, if the fovea is spared.
- Other measures of visual function are known to be abnormal in intermediate AMD and GA and have been suggested as clinical endpoints,
  e.g. contrast sensitivity, dark-adaptation, and visual field deficits
- For the use in clinical trials with a regulatory and patient access intention, candidate clinical endpoints need to be
  - systematically validated
  - in adequate patient populations
  - to be acceptable for regulatory authorities, Health Technology Assessment (HTA) bodies, and payors.

Need for public-private collaboration

- **Pharmaceutical companies**: Expertise in clinical drug development, requirements for clinical endpoints acceptable to regulatory agencies, HTA bodies, and payors.
- **Academic institutions**: Expertise in methods to assess visual function, structural pathologies and patient-reported health beyond BCVA.
- **Academic or Contract Research Organizations**: Experience in lean/ efficient setup and conduct of clinical trials according to global standard regulations.
- **Imaging and medical device companies**: expertise in the development and application of contemporary, state-of-the-art imaging methods.
- **Patients/ patient organization, users and caregivers:** important role in establishing utility, acceptability and value of new clinical endpoints.

Objectives of the full project

- **Validation of clinical endpoints and biomarkers**
  for intermediate AMD and progression to late stage AMD complicated by GA in appropriately designed and sized clinical trials
  - Assessment of **functional impairment** beyond BCVA
  - Measures of patient-reported health.
  - Identification of structural imaging biomarkers as surrogate markers of functional impairment of vision.
- Focus on state-of-the-art methodologies
  - no *de-novo* development of technologies since project phase only 5 years
  - and no molecular biomarkers

Pre-competitive nature

- Topic of this project is clinical validation of assessments of visual function as clinical endpoints beyond BCVA in intermediate AMD and the progression to late stage AMD.
- Currently, there are no compounds in late stage clinical development for these important disease states.
- Validated functional and imaging endpoints as well as measures of patient-reported health will enable clinical research of public and private researchers.
- This will allow to speed up the development process in these important and potentially blinding conditions.

Expected impact on the R&D process

The project targets to

- Generate clinical data, which would result in the acceptance of the novel clinical endpoints by regulators and payors.
- Enable future studies with new therapeutic agents using the newly establised endpoints. This would positively impact all clinical development phases from early, proof-of-concept studies through late stage phase 3 studies.
  - Endpoints would allow decision making on prioritizing promising candidate drugs for further clinical development
  - Significant acceleration of the development process
  - Including patient releveance of changes

Suggested architecture of the project

- Efficient and lean organization of this mainly clinical project is considered a challenge. A project structure with 5 working packages is suggested to applicants (for details see backup).
  - Working Package 1: Clinical Trials
  - Working Package 2: Functional Endpoints
  - Working Package 3: Patient-Reported Health/Health Economy
  - Working Package 4: Anatomical and Imaging Endpoints
  - Working Package 5: Project Management

Expected contributions of the applicants

- Expertise: Multidisciplinary consortium with proven track record in dry AMD research
  - strong practical expertise in the successful conduct of international multicentre trials in ophthalmology.
  - strong expertise in assessment methodologies for functional impairment other than BCVA.
  - strong expertise in state-of-the-art ophthalmological imaging techniques including approaches of multimodal imaging.
  - strong expertise in the establishment and validation of measures of patient-reported health, e.g. patient-reported outcomes in ophthalmology.
  - expertise in successful interactions with regulators and/or payors, e.g.in conduct of a EMA qualification procedure for novel methodologies in clinical research and health economic expertise.
  - expertise in project management in the context of IMI grants.

Expected (in kind) contributions of EFPIA members

- The industry consortium will comprise the following pharmaceutical and imaging companies:
  - Bayer Pharma AG (Leader)
  - Novartis (Co-Leader)
  - Janssen-Cilag Ltd
  - Roche
  - Zeiss
- Specialists from the industry consortium in the field of clinical endpoint development, patient-reported health, health economics, clinical trial design and drug regulatory procedures will actively participate in all project working packages with their specific expertise.

innovative medicines initiative

What's in it for you?

- To be part of a team that will make game-changing contributions to the way clinical research will be carried out in dry AMD
- Establish an innovative clinical trial program to validate functional endpoints, their anatomical correlates and their significance for patients.
- Provide input to regulatory authorities and payors on the relevance of vision impairment beyond BCVA in dry AMD, optimally resulting in adoption of these endpoints for regulatory clinical trials.
- Generate a toolbox of various, optimally interlinked (e.g. functional <-> structural, functional <-> patient-reported) endpoints with relevance for patients.
- Future use of the established endpoints in studies initiated by public researchers or pharma.

imi innovative medicines initiative

Key Deliverables of the Full Project - I

I. Development of clinical endpoints for impaired visual function beyond BCVA

- Comprises **validation** of
  - functional clinical endpoints as measures of functional visual impairment beyond BCVA in patients with
    - intermediate AMD
    - progression from intermediate AMD to late stage AMD with GA.
- To allow for use in health economic models, utility measures based on the functional impairments observed need to be developed.

Key Deliverables of the Full Project - II

II. Development of measures of patient-reported health

- Development of measures like patient-reported outcomes
  - Other approaches for covering patient-reported health, e.g. observer-reported outcomes, test of visual function in virtual realities or other tests would be considered, if the scientific rationale and potential for regulatory acceptance of such measures would be sufficiently justified.
- Measures of patient-reported health need to be established and at least content validated.
- Not only patients with intermediate AMD but also with the neighboring disease states, i.e. early AMD and manifest GA, need to be included for this objective.

Key Deliverables of the Full Project - III

III. Correlation of functional assessments of impaired vision with structural deficits assessed with state-of-the-art imaging methodologies

- Structural/Imaging endpoints as surrogate markers of current or future functional deficits, which could be used as endpoints in clinical trials.
- Multimodal imaging is encouraged.

Questions?

Contact the IMI Programme Office
infodesk@imi.europa.eu • www.imi.europa.eu

www.imi.europa.eu
@IMI_JU

Backup – Working Packages

www.imi.europa.eu
@IMI_JU

Suggested Working Packages

- **All WP leads should work jointly together in the setup and conduct of the clinical trial(s) of this project to**
  - **fully recruit the trial(s) in the given time,**
  - **to generate data of sufficient quality for meaningful analyses, and**
  - **to crosslink findings especially of WP 2-4**.
- Functional assessments (WP1, 2) need to be correlated with
  - anatomical/structural findings to establish and validate biomarkers with the potential to substitute for functional assessments and vice versa (WP2, 4);
  - with patient-reported health to support and confirm that abnormalities in test of functional deficits are meaningful to patients (WP2, 3).

imi innovative medicines initiative

WP 1: Clinical Trials

- Platform for Clinical Trial Conduct including:
  - Trial setup, monitoring, setup of electronic case report forms (eCRF)s and of the clinical database setup and data management. In addition it includes clinical trial statistics to develop and perform analyses of clinical trial data according to a statistical analysis plan (SAP) plus exploratory analyses.
- Regulatory:
  - Regulatory interactions (with EMA and if possible with US FDA, preparation and conduct together with EFPIA consortium)
    - To clarify appropriateness of the clinical trial concept for regulatory acceptance of the proposed endpoints
    - Targeted: EMA qualifications procedure to support novel methodologies

WP 1: Clinical Trials ctd.

- Genetic Risk Factors and Biobanking in the clinical trial(s):
  - Not main focus of this call topic
  - Patient collectives may be tested for known genetic factors of disease and correlation to specific functional impairments may be assessed.
  - No *de novo* search for novel genetic risk factors
  - Biobanking efforts should be put into perspective with the overall budget and needs to have no meaningful negative budget impact on the other WPs.

WP 2: Functional Endpoints

- Local evaluation of functional assessment results plus evaluation of these assessment data by a central evaluation unit for quality control and standardization of local assessments;
- **Optional**: to develop automated or semi-automated assessment algorithms on top of existing analysis software based on existing data or data from the clinical trials to further facilitate use of the functional endpoints in clinical practice;
- For proposal: applicant consortia need to provide a detailed list and scientific justification with prioritization of the functional endpoints intended for evaluation.
- Exploration of structure-function relationships together with WP 3/4

WP 3: Patient-Reported Health and Health Economy

- Establishment and content validation of patient-reported health in dry AMD;
- Correlation of measures of patient-reported health with functional assessments;
  - Following existing regulatory guidance for development of measures of patient-reported health, e.g. the US-FDA guidance on patient-reported outcome measures. (U.S. FDA, 2009);
- Establishment of utility measures jointly with WP 2 to allow for health economic modelling beyond BCVA.

WP 4: Anatomical and Imaging Endpoints

- Analysis of Images from clinical trials using established standard imaging modalities plus novel, innovative technologies.
  - Experienced central reading centers (CRCs)
  - Imaging devices used are either already commercially available or are market-ready prototypes which will be commercially accessible in the near future.
- Multimodal image correlation is encouraged.
- Correlation of imaging pathologies with the outcome of functional assessments is mandatory.
- **Optional**: semi-automated or automated imaging analysis within the framework of the overall project.
- No de novo development of imaging technologies.

Working Package 5

- **Work Package 5: Project Management**
- Lean Project Management to fulfil requirements of IMI JU in respect to distribution and reporting of funding.

Contact IMI

infodesk@imi.europa.eu

www.imi.europa.eu

@IMI_JU