Innovative Medicines Initiative

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1st Call for Proposals 2014

Innovative Medicines Initiative 2

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INTRODUCTION

The Innovative Medicines Initiative 2 (IMI2) Joint Undertaking has been created[1] following the below principles:

- Research related to the future of medicine should be undertaken in areas where societal, public health and biomedical industry competitiveness goals are aligned and require the pooling of resources and greater collaboration between the public and private sectors, with the involvement of small and medium-sized enterprises (SMEs).
- The scope of the initiative should be expanded to all areas of life science research and innovation.
- The areas should be of public health interest, as identified by the World Health Organisation report on priority medicines for Europe and the World (2013 update: http://www.who.int/medicines/areas/priority_medicines/en/).

The initiative should therefore seek to involve a broader range of partners, including mid-caps[2], from different sectors e.g. biomedical imaging, medical information technology, diagnostic and/or animal health industries (while ensuring gender matters are considered). Involving the wider community in this way should help to advance the development of new approaches and technologies for the prevention, diagnosis and treatment of diseases with high impact on public health.

The IMI2 Strategic Research Agenda (SRA) is the main reference for the implementation of research priorities for IMI2. Based on the SRA the 2014 scientific priorities for IMI2 have been prepared, which include themes on metabolic disorders and neurodegeneration which are addressed in this call.

Applicant consortia are invited to submit short outline proposals to one of the topics. These proposals should address all aspects of the topic to which the applicant consortia are applying. The size of each consortium should be adapted to the scientific goals and the expected key deliverables.

While preparing their short outline proposals, applicant consortia should ensure that needs of patients are adequately addressed and, where appropriate, patient involvement is encouraged. Synergies and complementarities with other EU funded projects should be explored in order to avoid overlaps and duplications and to maximize European added value in health research.

[1] The Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking.

[2] Under the IMI2 JU, mid-sized companies having an annual turnover of EUR 500 million or less, established in a EU Member State or an associated country, are eligible for funding.

Before submitting a short outline proposal, applicant consortia should familiarize themselves with all call documents such as the IMI2 Manual for evaluation, submission and grant award, and the IMI2 evaluation criteria.

1. TRANSLATIONAL APPROACHES TO DISEASE MODIFYING THERAPY OF TYPE 1 DIABETES MELLITUS (T1DM)

BACKGROUND AND PROBLEM STATEMENT

The global prevalence of diabetes has risen dramatically over the past decades. Whilst the connection between change in lifestyle patterns and type 2 diabetes mellitus (T2DM) seems undisputed, the connection between increased urbanization and type 1 diabetes remains a conundrum. Type 1 diabetes mellitus (T1DM) is a chronic disease affecting worldwide around 17 million people (World Health Organization's Priority Medicines for Europe and the World 2013 update, p.88). Type 1 disease has its peak incidence at puberty, but may occur at any age. The incidence rate is highest in Europe affecting altogether 22/100.000 per year, with major regional differences and an overall 25% higher incidence rate than in the United States of America (USA) (www.diapedia.org). The incidence of childhood T1DM is rapidly on the rise worldwide, especially in the under 5 year old age group.

T1DM is characterized by hyperglycemia due to destruction and loss of insulin-producing pancreatic beta cells and function over time. Furthermore, T1DM can be differentiated from the more common T2DM based on one or several autoantibodies directed towards antigens of the endocrine pancreatic islets. The emergence of islet autoantibodies as biomarkers preceding clinical islet beta cell failure has led to the generally held view that T1DM is an autoimmune disease and that immunologic abnormalities occur well ahead of clinical onset. The precise cause of type 1 diabetes is unknown, and believed to be due to one or more of the following: genetic susceptibility, dysfunctional programming of immune tolerance, diabetogenic trigger(s) and/or exposure to a driving antigen. Recent analyses of pancreatic autopsy specimens from individuals with longstanding T1DM surprisingly demonstrate a heterogeneous but unexpected persistence of residual pancreatic beta cells despite insulin deficiency and active autoimmunity. These unexpected findings highlight the need for additional translational research to enable a deeper understanding of the pathophysiology, heterogeneity, and natural history of T1DM in humans.

The disease is currently not preventable and no cure is available. The only available pharmacotherapy for T1DM patients is the lifelong injection of insulin. Management of T1DM is not trivial as it is associated with multiple daily "finger pricks" to control blood glucose and requires multiple injections of insulin replacement therapy. A significant further burden is the risk of insulin induced hypoglycaemia which is currently considered

the most significant barrier for optimization of adherence. An alternative approach to subcutaneous insulin replacement therapy is pancreas or pancreatic islet cell transplantation but existing cell replacement therapies require immunosuppression and are limited to very few recipients.

NEED AND OPPORTUNITY FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

For almost a century, pharmacotherapy of T1DM has been synonymous with insulin therapy. Although undisputedly very successful, insulin therapy is associated with recognized limitations, such as adherence and drug induced hypoglycaemia. Stakeholders involved in care of people with T1DM as well as patients themselves agree that truly disease modifying therapy remains the ultimate approach to solve the challenge. Very few experimental alternatives to insulin therapy have been approached and clinical experimentation in the field of T1DM care has been modest at best. Considering the rapid growth of T1DM prevalence and the gravity of the problem, stakeholders in the T1DM community agree that is about time to intensify innovation in the field of T1DM therapy.

The pharmaceutical industry represented through EFPIA is highly motivated to play a leading role in establishing the widest possible cross-functional consortium with representatives from patient advocacy groups, health authorities, diabetes care givers, innovators, and industrialists. The objective is clearly to launch discovery programs in the field of T1DM that could lead to prevention as well as disease modifying and ultimately curative therapy. To achieve this ambitious goal deeper insight into the heterogeneous, phenotypic characteristics of people either at risk of developing T1DM or having manifest disease is required. This goal can only be achieved by pooling the knowledge, expertise and resources of all key stakeholders in the area, both public and private. Using state of the art technologies it is envisioned that this initiative will focus on a complete mapping of interactions between the immune system and pancreatic beta cells in humans and on the environmental changes that has led to increased disease incidence.

Through a thorough mapping of environmental and molecular mechanisms leading to T1DM, it will become possible to draft preventive strategies and to design future disease modifying therapies. The research strategy of the call shall embrace a strong focus on translational medical activities initiated at the bedside, refined at the workbench, and then finally brought back to the bedside for clinical validation of potential therapeutic approaches aiming at fundamentally preventing, halting, and reversing the β-cell destructive course of T1DM.

OVERALL OBJECTIVES

The overall aim of the initiative is to significantly progress the understanding of T1DM disease by bringing together patients, health authorities, leading clinicians, and researchers from the areas of immunology, beta cell biology, and biomarker research from both academia and industry.

Based on the assumption that T1DM is primarily driven by immunological dysfunction leading to beta cell destruction, it is expected that this initiative will significantly progress the understanding of the pathophysiology, heterogeneity, and natural history of T1DM in humans.

Translational medicine efforts mapping all stages of the disease are considered a pre-requisite for the initiation of rational drug discovery programs. As the program progresses, leading to the formulation of hypotheses of central pathophysiological processes in the development of T1DM, it is envisioned that the consortium will initiate clinical experimental studies that focus on validation in clinical studies of the newly acquired insights of dysfunctional molecular pathways leading to manifest T1DM.

POTENTIAL SYNERGIES WITH EXISTING EU SPONSORED CONSORTIA

It is expected that the project generated by this call will synergise and build on the results and assets of previous and ongoing European effort in diabetes including IMI projects in the diabetes area. The IMIDIA project (http://www.imidia.org/) has established a unique standardized, continuously growing human biorepository of biofluids (plasma, serum), pancreatic tissue and pancreatic beta cells from mostly adult diabetes and non-diabetic control subjects (predominantly T2DM).

The DIRECT project (http://www.direct-diabetes.org/index.php), while focussing on type 2 diabetes also is establishing a comprehensive collection of biosamples and clinical information on non-diabetic control subjects that can be of high value for the T1DM call.

In addition synergies with FP7-supported consortia in the fields of T1DM can be seen, e.g. to BIOSID (http://ec.europa.eu/research/health/medical-research/diabetes-and-obesity/projects/biosid_en.html), DIABIL_2 (http://www.diabil-2.eu/), DIABIMMUNE (http://www.diabimmune.org/), DIAMAP (http://www.diamap.eu/), DIAPREPP (http://www.diaprepp.eu/), NAIMIT (http://naimit.eu/), PREPOBEDIA (http://www.prepobedia.org/).

In addition synergies in the field of type 1 diabetes could be established with BBMRI (http://bbmri.eu/).

Another important synergy can be envisaged with the efforts of the global TRIALNET initiative (https://www.diabetestrialnet.org/about/index.htm).

The JDRF nPOD resource (http://www.jdrfnpod.org) of tissues (pancreas and other organs) from donors with diabetes, at-risk of developing T1DM, as well as non-diabetes controls, will also synergize with the efforts of this program.

EXPECTED KEY DELIVERABLES

Disease Biology and Translational Medicine (Target & Biomarker Identification)

It is envisioned that a pan-European clinical trial and translational research network will be built, including creation of a T1DM patient registry of readily accessible cohorts of T1DM patients willing to participate in future clinical research in the field. The network will facilitate a systematic and comprehensive functional and molecular profiling of disease heterogeneity, and identification of high-risk subjects beyond the use of islet-autoantigens.

The expanding on existing patient registries and prospective cohorts as well as the establishment of new cohorts shall be used to focus on:

- Systematic prospective and retrospective launch of broad "–omics" characterization of human biological samples from newborns/infants/children/adolescents/adults at risk of developing diabetes as well as from newly diagnosed T1DM patient cohorts undergoing standard glucose control therapy. Such "full –omics" analysis should include both "at risk" subjects (HLA+AA-, HLA+AA+), as well as new onset T1DM patients to identify molecular markers in patient biofluids (blood, plasma, serum, lymph, urine)
    - Transcriptome assessment from enriched cells / particular fluid samples (including short RNAs and microRNA profiling)
    - SNP mapping & eQTL analysis, next generation sequencing of fast progressing, "at risk" subjects
    - Analysis of the gut microbiome
    - Metabolomics assessment (from available biofluids)
    - Proteomics and phosphoproteomics assessment (from exosome/biofluids)
    - Systematic epigenetic analysis (incl. methyl- & acetylation profiles).
- Phenotypic characterization (in silico based on medical records, as well as through active experimental clinical studies)
    - Identification of the glucose responsiveness as an indicator for patient beta cell status (OGTT, fasting blood sugar, hypoglycaemia propensity)
    - Pilot studies of imaging pancreatic inflammation
    - Behavioural phenotypes (therapeutic adherence, dietary preferences, exercise, cognitive)
- Establishment of systematic large-data and bio-bank repositories enabling extensive cross functional data mining and modelling of disease incidence and progression.

- Long term glucose control (HbA1c) status in recent onset patients as well as in relevant controls
- Exploration of imaging technologies for the use of identification and stratification of high-risk patients and as a surrogate end point in clinical studies.

Further activities could embrace novel methods to measure auto reactive T cell functional responses. Characterization of leukocytes obtained from patient blood, lymph or tissue samples to identify immune cell targets and surrogate end points are desired. A goal will be to define, standardize, and ultimately approve biomarker and immune profiling analysis that could be implemented for staging participants in future T1DM clinical trials in Europe. Prerequisite for successful outcome of such standardization effort is active participation of innovators, regulatory authorities, health care providers, and patient representatives.

In parallel, the project must focus on the metabolic characterisation of T1DM patients, such as the status of ß-cell function, or changes and defects in β-cell proliferation mechanisms (glucose, glucokinase, PDGF(R), WNTs), and beta cell stress/death in people with T1DM. Leveraging and enabling access to human pancreatic beta cells, islets, and pancreatic tissue from T1DM patients, through direct or collaborative efforts, should be prioritized by the consortium. In some instances implementation of surrogate assays of immune system interaction with islet function may be required, and it is suggested that the consortium integrate learnings from previous IMI and EU funded projects.

Qualification of identified biomarkers as diagnostics, as well as detailed characterization of the prediabetic period using novel diagnostics such as implantable micro-devices and early detection of autoantibodies (“Lab on a chip“) should be considered. Innovation of technically viable diagnostics solutions may require involvement of specialized entrepreneurs not traditionally represented by EFPIA members. Identification and validation of biomarkers reflective of the disease progression including β-cell specific “ID tag” to quantify/monitor beta cell mass is also of high interest as it will assist novel disease taxonomy.

Defining and refining disease taxonomy for T1DM may create the foundation for personalized therapy of T1DM by the use of novel biomarker candidates and imaging technologies for the identification and stratification of high-risk patients and as a surrogate end point in clinical studies (consolidate health authority acceptance of T1DM disease classification as basis for medical decision making and approval of novel T1DM therapies).

Furthermore, the initiative will consider the development and characterization of most translatable preclinical T1DM models for discovery of novel clinical therapies to verify the newly acquired molecular knowledge for their human disease translatability.
Translational medicine efforts mapping all stages of the disease are considered a pre-requisite for the initiation of rational drug discovery programs aiming at treating the underlying causes of β-cell failure in people with T1DM.

Innovative clinical trial paradigms

During the past decade, a limited number of clinical trials have tested a variety of therapeutic approaches aimed at modifying immune function in people at risk for developing T1DM or with manifest disease. Therapeutic approaches have included attempts to induce immune tolerance to known islet autoantigens (proinsulin, GAD65), immune suppression through T cell modifying therapies (eg anti CD3), and anti-inflammatory antibodies (eg anti-Il-1β and anti-TNFα). These therapeutic approaches have been characterized by highly diverse clinical trials protocols and inconsistent primary end-points, rendering direct comparisons of efficacy and safety difficult. Guided by translational insights to the disease, the program is expected to facilitate the development of standardized clinical trial protocols with clearly defined, clinically meaningful, evidence based end-points providing indisputable medical value for people with T1DM as well as society.

As it is expected that the thorough characterization of “at risk” populations and newly diagnosed T1DM patients will consolidate existing as well as spur novel hypotheses for T1DM aetiology and pathophysiology, a clinical trial network shall also be used as vehicle for clinical research aiming at validating potential novel therapies.

Existing evidence suggest that a highly targeted T-cell mediated immune response is responsible for the islet destruction seen in T1DM. Therefore, modelling sequential T cell activation, T cell mediated cytotoxicity, and dysfunctional T cell regulation has led to a number of possible immunomodulatory approaches that have yet to be tested in people with new onset T1DM. In particular, in silico modelling based on in vitro and on animal data suggest that sequential combination of immunomodulatory agents (T cell specific antibodies, modulators of chemotaxis, inducers of immunological tolerance) may provide rational approaches for clinical trials aimed at halting the progression of the immune based destruction of beta cells and ultimately inducing tolerance to the triggering autoimmune event. It is expected that the established clinical trial network will engage in testing such novel immunomodulatory and tolerance inducing principles. The following deliverables are envisioned:

- Generation of a European comprehensive network of clinical and translational research centres capable of recruiting and conducting clinical trials in people with T1DM (providing a prospective clinical trials database for T1DM).
- Development of standardized entry criteria and endpoints for T1DM trials (both metabolic and immune profiles) preferably in collaboration with clinical centers in the US and with participation of patient advocacy groups, and regulatory authorities.
- Implementing the use of electronic data capture devices to collect an array of "real world data" useful for verification of therapeutic area hypotheses, regulatory rapports, etc.
- Testing and development of novel bio-statistical methodologies applicable to new compositions of relevant end points for T1DM clinical trials.
- Evaluation of novel mono- and combination approaches (i.e. combining multiple immune modulatory approaches, immune cell migration modification, immune tolerance inducers, β-cell enhancing therapeutics) in people with T1DM.
- The pan-European clinical trial and translational research network is expected to make important contributions to the evaluation of new emerging biomarkers and diagnostics indicative of T1DM disease progression or disease modification in clinical settings.

Patient participation

To aid in making the projects generated by this call more patient-centric, the project will be expected to establish a T1DM Patient Advisory Committee to enable input from patients and family members into the research involving subjects with T1DM and their biosamples and research around the development of innovative clinical trial paradigms. The T1DM Advisory Committee should include patients with T1DM of varying age and varying duration of disease, individuals at-risk of developing T1DM, and family members of children and adults with T1DM.

INDUSTRY CONSORTIUM

From the pharmaceutical industry consortium it is expected that specialists from the areas of molecular biology, chemistry, biologics, preclinical & clinical pharmacology, bioinformatics, translational medicine and clinical trials will actively participate in the projects work packages.

EFPIA PARTICIPANTS AND ASSOCIATED PARTNERS

Sanofi (coordinator), Juvenile Diabetes Research Foundation (JDRF) (co-coordinator), Novo Nordisk, Eli Lilly, GSK, Helmsley Charitable Trust. The EFPIA partners have invited the JDRF and Helmsley Charitable Trust to participate as equal partners in the steering

group formulating this T1DM focused call. The JDRF (http://jdrf.org/) is a not for profit organisation focusing on patient advocacy as well as funding of research in the field of T1DM. The Helmsley Charitable Trust (http://helmsleytrust.org/) is a charitable organisation supporting research in health, selected place-based initiatives, education and human services. Both organisations participate in the present topic as Associated Partners to IMI2.
Additional companies are under consideration and the final list is to be confirmed.

INDICATIVE DURATION OF THE PROJECT

The indicative duration of the project is 84 month (7 years). This duration allows in depth systematic molecular analysis and immune and metabolic phenotyping of retrospective and prospective collected biological samples from T1DM patient cohorts. Further, the obtained insights will be integrated into novel to be established and existing models. Finally, the comprehensive patient characterization will be thoroughly integrated in to be defined prospective clinical trials.

FUTURE PROJECT EXPANSION

Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking, if so foreseen in the applicable annual work plan, may publish at a later stage another call for proposals restricted to those projects already selected under this call in order to enhance their results and achievements by extending their duration and funding. Consortia will be entitled to open to other beneficiaries as they see fit.

In the context of this topic, the EFPIA companies already envision the possibility to expand the project scope, during its implementation, to support clinical trials with immune-modulatory compounds in development. A restricted call would allow achieving this in the most efficient way by timely building on the progress and outcomes of the deliverables related to innovative clinical trial paradigms (e.g. clinical trial networks, identification of at risk patient population, definition of standardized entry criteria and endpoints, and novel bio-statistical methodologies for T1DM clinical trial). The detailed scope of the call will be described in the relevant annual work plan.

INDICATIVE BUDGET

The indicative contribution from EFPIA companies and Associated Partners is EUR 17 630 000.
The financial contribution from IMI2 JU will be a maximum of EUR 17 630 000.

Justification for Sanofi and JDRF non-EU in-kind contribution

Sanofi´s non-EU in-kind contribution amounts to EUR 3 000 000. Studies in preclinical models for the evaluation of the role of the autoimmune system in the development of T1DM are available at Sanofi sites based in the US (Genzyme). The inclusion of these autoimmune models in the project and the linkage of their results to the outcome from studies on beta-cell function are required to evaluate novel translatable preclinical models mimicking human T1DM. Comparable preclinical autoimmune models are not available at EU-based Sanofi sites. Furthermore, non-EU contribution will be generated by the partial manufacture of the autoimmune antibody that will be investigated in a clinical trial of the "Innovative Clinical Trial Paradigms in T1DM" part of the project.

JDRF non-EU contribution amount to EUR 420 000, to cover costs of their US based personnel.

TYPE OF ACTION

Research and Innovation action

APPLICANT CONSORTIUM

The applicant consortium is expected to address all the research objectives and make key contributions on the defined deliverables in synergy with the industry consortium.

To address the complex tasks of the call adequately, the project is expected to build a pan-European clinical trial and translational research network including a clinical registry of eligible people with T1DM. Such network will include:

- Academic endocrine clinics and associated supporting departments
- Basic, translational, and clinical researchers from the fields of T1DM autoimmunity and β-cell biology,
- Drug discovery and medical staff in Pharmaceutical Industry and Small and Medium size Enterprises.

- Hands-on data base specialists and big data managers
- Patient organizations/representatives
- Experts in regulatory science and health technology assessment preferably representing European health authorities.

Cross fertilization in this team of experts is the key for the success of the initiative.

SUGGESTED ARCHITECTURE OF THE FULL PROPOSAL

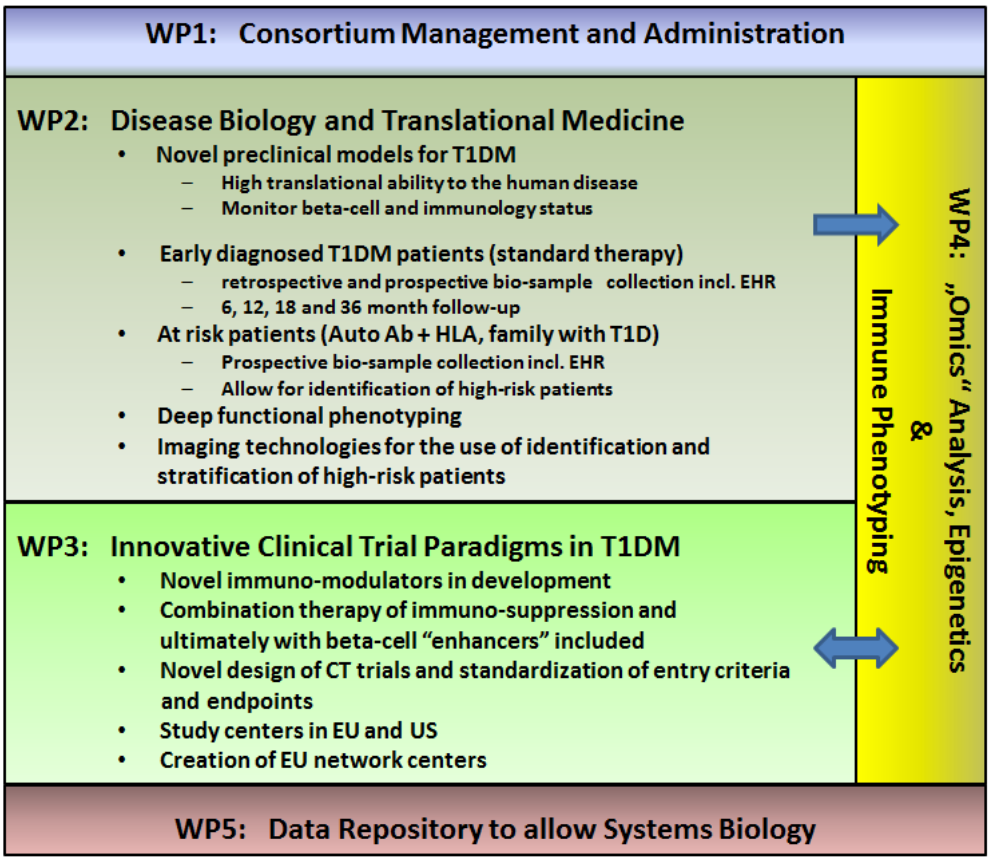
The above described cross functional and cross sector team members are recommended to work together in dedicated work packages addressing the different aspects of the overall call. Each work package team is recommended to consist of academic and industrial/biotech members with regular interactions to ensure knowledge exchange between the different expertises. Inter-work package knowledge transfer should be ensured at all times via regular management board meetings. The jointly used data documentation tool is considered a key piece for the success of the overall call ensuring maximum information gain by applying systems biology.
In addition a plan for interactions with Regulatory Agencies/Health Technology Assessment bodies with relevant milestones and appropriate resource allocation should be built into the project architecture as well as aspects related to dissemination and sustainability, facilitating continuation beyond the duration of the project.
Please also note that the following outline of the architecture for the full proposal is a suggestion; different innovative project designs are welcome, if appropriate.

Note: Data collection and data management should be conducted according to established data standards and/or in collaboration with a data standards organization (e.g. CDISC), to develop new data standards if no established data standards exist.

Suggestion for project structure

This project is suggested to be organized in 4 major work packages:

- WP2: Disease Biology and Translational Medicine
- WP4: “Omics” Analysis, Epigenetics and Immune Phenotyping
- WP3: Innovative Clinical Trial Paradigms in T1DM
- WP5: Data Repository to allow Systems Biology



As a result of this, the project will:

- significantly progress the understanding of the pathophysiology, heterogeneity and natural history of T1DM in humans,
- improve the knowledge on translatable preclinical models for T1DM,
- facilitate the development of standardized clinical trial protocols with defined clinically relevant, evidence based entry- and end-point criteria and the evaluation of novel mono & combination treatment approaches.

2. DISCOVERY AND VALIDATION OF NOVEL ENDPOINTS IN DRY AGE-RELATED MACULAR DEGENERATION AND DIABETIC RETINOPATHY

BACKGROUND AND PROBLEM STATEMENT

Diseases of the retina are among the leading causes of blindness world-wide. Substantial progress has been made in the treatment of neovascular age-related macular degeneration (neovascular AMD) and diabetic macular edema (DME). However, for other common retinal conditions such as the dry form of AMD (dry AMD) or diabetic retinopathy (DR) treatment options remain limited. One major development hurdle is the lack of suitable, patient-relevant study endpoints with clinical relevance both in early exploratory and pivotal trials. Moreover, there are significant gaps in the understanding of how pre-clinical findings translate into outcomes. This results in the following problem statements:

- Best corrected visual acuity (BCVA) and derived variables are the only endpoints that have served as basis for regulatory approval of retinal drugs. However, BCVA captures only a small portion of visual function. Dry AMD or DR patients may have good BCVA, in spite of significant clinical impairment resulting in difficulties with daily activities such as reading or driving. There is a lack of methodology/instrumentation to quantify this type of vision impairment robustly and reliably.

- There is a lack of short-term endpoints predictive for visual acuity outcomes that would qualify as sufficiently predictive proxy in an early proof-of-concept or dose-finding study or even as surrogate endpoints in pivotal trials.

- There is a lack of predictive markers and models (animal models and cellular systems) translating from the preclinical to the clinical setting. It needs to be evaluated to what extent novel visual function measures will translate from pre-clinical to clinical studies as well as to what extent preclinical effect sizes will translate into clinical effects.

- There is a gap in understanding of endophenotypes in diseases like dry AMD or DR that are currently perceived as close disease entities, but in reality may have very different natural courses or response to therapy. This may have significant medical and health-economic implications.

In ophthalmology there are many and very diverse techniques that allow to measure functional and anatomic parameters. Despite this methodological wealth, the relevance of different parameters for the assessment of disease severity remains uncertain, and so does their translation into outcomes relevant for patient daily activities and Quality of Life (QoL). For example, in neovascular AMD and other well-evaluated indications, it has been shown that many promising imaging parameters are weakly or not-at-all correlated with patient relevant visual function. It is obvious that significant methodological validation work needs to be done. Therefore, an important focus on endpoint research is to validate existing technologies and to leverage the large armamentarium of contemporary ophthalmological examination techniques.

NEED AND OPPORTUNITY FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

The topic tackles a problem of a scale that cannot be achieved by a single institution and requires combination of expertise and collaboration of stakeholders across different sectors:

- **Pharmaceutical companies** have expertise of drug discovery, drug development as well as regulatory and HTA requirements.
- **Academia** has expertise in methods to assess visual function and structural (bio-) markers that may correlate with visual impairment both pre-clinically and clinically. They have access to databases on the natural history and the course under treatment of the diseases in-scope that would allow a retrospective analysis of potential correlations.
- **Imaging and medical device companies** have expertise in development and application of contemporary examination methods.
- **Hospitals/practicing physicians** have access to dry AMD and/or DR patients. They have a good understanding of epidemiology, pathophysiology, or other evidence to predict clinical benefit.
- **Patients, users and caregivers** can also play an important role in the establishing the value of new endpoints.
- **Regulators, Health Technology Assessment (HTA) bodies and payers** could provide guidance on prerequisites for acceptability of endpoints.
- **Others such as technological centres and Contract Research Organisations** may be able to contribute to the deliverables of the project.

OVERALL OBJECTIVES

The aim of the project is to evaluate novel endpoint candidates for dry AMD and DR for use in clinical trials investigating drug or other therapies. The evaluation should cover the technical, medical and health economic appropriateness of a method and bridge preclinical and clinical studies. The following methods are in scope:

- **Novel approaches to subjective visual function testing beyond BCVA:** Methods falling into this category include methods of visual acuity testing under different conditions such as dim light or low contrast. Additional methods may comprise parameters such as microperimetry, motion or pattern detection, contrast sensitivity, color vision, visio-motor coordination or reading speed. The main research objective on this type of endpoints is the validation of patient relevance and/or predictive strength for each potential endpoint.
- **Electrophysiology:** Electrophysiological methods offer a broad array of largely objective parameters to quantify visual function. They are less dependent on patient co-operation than subjective visual function tests. Electrophysiological methods can be used in animal models and as such they have an inherent potential in translational research settings. The key objective of electrophysiological studies is the translation of pre-clinical results into clinical outcomes as well as correlation with patient-relevant endpoints.
- **Imaging:** Imaging devices that quantify anatomic changes in the retina have evolved tremendously in the last decade and have revolutionized disease diagnosis and monitoring. The further development of the techniques by means of image processing, detectable biomarkers in the retina and potentially photonics will further change the diagnostics and follow-up of retinal diseases. It would be important that such parameters are put into perspective and correlated to patient-relevant outcomes and prognosis of the disease.
- **Patient reported outcome (PRO) tools and QoL-related endpoints:** There are few validated PRO tools and the most prominent example, the NEI-VFQ-25[3], is only well-correlated to the BCVA of the better-seeing eye, therefore being of little additional value. Studies in that field should focus on development of better-designed and researched PRO tools capturing the patient-relevant impact of visual impairment, beyond visual acuity.
- **Soluble and genetic biomarkers:** Several soluble and genetic biomarkers correlate with progression of diabetes and its complications as others do with age-related-macular degeneration. Activities in this field should focus on putting these and novel

[3] National Eye Institute Visual Functioning Questionnaire 25 (www.nei.nih.gov)

markers like proteomic and metabolomics biomarkers into perspective with outcomes, prognosis and severity of the ocular disease.

- **A combination of the aforementioned methods:** The consensus is that the likelihood of a single method fulfilling all the above criteria is low and therefore research on combinations of the aforementioned approaches will be required.

POTENTIAL SYNERGIES WITH EXISTING CONSORTIA

Synergies and complementarities with existing initiatives, both in Europe and globally should be considered, building on achievements, and incorporating when possible data and lessons learnt, while avoiding unnecessary overlapping and doubling of efforts.

Applicants should include considerations in their proposal how the interactions with ongoing consortia, such as the following ones, are envisaged.

The SUMMIT is an ongoing IMI project on diabetes complications (http://www.imi.europa.eu/content/summit; www.imi-summit.eu). One of the work packages is dedicated to characterisation of retinal phenotype in diabetic patients and thorough documentation of the eye status along with the status of the systemic condition (including soluble bio-markers). There are clear opportunities for synergies with this project.

In addition, there are potential synergies with on-going FP7 projects within the field of macular degeneration and diabetic retinopathy, for example, HELMHOLTZ[4], ENDHOMRET[5] and REDDSTAR[6].

The proposal should also build on achievements and learnings from any relevant European and Member state initiatives and aim to create synergies with H2020 generated projects and global initiatives.

EXPECTED KEY DELIVERABLES

The key deliverable will be the generation of adequate data resulting from robust retrospective and/or prospective studies in patients that could serve as basis for initial discussion with regulatory agencies and/or HTA-bodies for acceptance of the resulting outcomes as endpoints for future clinical programmes. Interactions and advice from regulatory authorities will be sought early-on during set-up of the studies.

It is expected that the proposed research programme delivers data for each of the proposed conditions on:

[4] http://www.vision-research.eu/index.php?id=909
[5] http://erc.europa.eu/erc-funded-projects
[6] http://www.reddstar.eu

- Technical evaluation of potential methods in regards to validity, repeatability, reliability, interpretability, and translatability from preclinical to clinical. The technical evaluation includes also an assessment whether a method is acceptable for patients with the disease.
- Development of novel methods (e.g. imaging, proteomics, metabolomics, genomics, epigenetics) and models, including animal models, and tools as applicable (e.g. disease/endophenotype specific patient reported outcome tools or novel visual function testing protocols).
- Clinical validation of methods/tools in patient studies for dry AMD and DR. Preferentially, the studies should evaluate several candidate methods head-to-head. The collection of biomarkers (e.g. genomic or soluble biomarkers including proteomic and metabolomics markers) during the study will permit to explore the selection of high risk populations.

It is expected that each proposed study focuses either on a translational aspect or on patient-relevance of a given outcome parameter or combines both if applicable. If translational aspects are studied, the investigation should be set-up to show the correlation of data from an experimental model with the clinical outcome parameter. For studies aiming to show patient-relevance, a concept should be provided on how to link the novel parameter to an accepted parameter (e.g. a PRO tool), either previously validated or to be validated within the proposed project.

Wherever there are synergies between dry AMD and DR these should be leveraged, e.g. by combining both conditions within one study. However, it is also important to clearly address how the applicant consortium intends to investigate condition-specific aspects.

INDUSTRY CONSORTIUM

The industry consortium will comprise pharmaceutical and imaging companies. Industry contribution will include study support with central study functions (data management, statistics, project/study management, regulatory etc.).

EFPIA PARTICIPANTS

Bayer HealthCare (coordinator), Sanofi, Novo Nordisk, Zeiss

INDICATIVE DURATION OF THE PROJECT

The indicative duration of the project is 5 years (60 months).

INDICATIVE BUDGET

The indicative EFPIA contribution is EUR 7 000 000.
The financial contribution from IMI2 JU will be a maximum of EUR 7 000 000.

TYPE OF ACTION

Research and Innovation action

APPLICANT CONSORTIUM

The applicant consortium is expected to address all the research objectives and make key contributions on the defined deliverables in synergy with the industry consortium.
The applicant consortium is expected to be multidisciplinary and have a proven track record of:

- Strong clinical expertise in ophthalmology (including advanced examination techniques)
- Strong clinical research experience
- Access to patients and databases
- Public health expertise
- Health economic expertise
- Understanding of pre-clinical models in ophthalmology
- Biomarker expertise (biomarkers research and development)
- Data and knowledge management
- Regulatory, ethics, patients and project management.

It is intended that an advisory panel to the consortium, which comprises payers, regulatory agencies and other relevant expert advisors is instituted for this project.

The contribution from the applicant consortium should be the setting-up and running of the studies that are required to meet the call's objectives. These activities will be supported by in-kind and financial contribution from the EFPIA companies.

SUGGESTED ARCHITECTURE OF THE FULL PROPOSAL

The consortium is expected to suggest architecture for the full proposal addressing all objectives and key deliverables.

A plan for interactions with Regulatory Agencies/health technology assessment bodies with relevant milestones, and appropriate resources allocation, should be built into the project architecture as well as aspects related to dissemination and sustainability, facilitating continuation beyond the duration of the project.

Note: Data collection and data management should be conducted according to established data standards and/or in collaboration with a data standards organization (e.g. CDISC), to develop new data standards if no established data standards exist.

CONDITIONS FOR THIS CALL

Applicants intending to submit a short outline proposal in response to the IMI2 Call 1 should read the topic text, above, the IMI2 Manual for submission, evaluation and grant award and the IMI2 Evaluation Criteria.

Call Identifier: H2020-JTI-IMI2-2014-01

Publication Date: 9 July 2014

Stage 1 Submission start date: 9 July 2014

Stage 1 Submission deadline: 12 November 2014 – 17:00:00 Brussels time

Stage 2 Submission deadline: 14 April 2015 – 17:00:00 Brussels time

Indicative Budget: From EFPIA and Associated Partners: EUR 24 630 000
From the IMI2 JU: EUR 24 630 000

IMI2-2014-01-01	The indicative contribution from EFPIA companies and Associated Partners is EUR 17 630 000. The financial contribution from IMI2 JU is a maximum of EUR 17 630 000	Research and Innovation action Two stage submission and evaluation process Only the applicant consortium whose proposal is ranked first at stage 1 is invited for stage 2
IMI2-2014-01-02	The indicative EFPIA contribution is EUR 7 000 000 The financial contribution from IMI2 JU is a maximum of EUR 7 000 000	Research and Innovation action Two stage submission and evaluation process Only the applicant consortium whose proposal is ranked first at stage 1 is invited for stage 2

Eligibility and admissibility conditions

The conditions are described in parts B and C of the General Annexes to the work programme.

Evaluation criteria, scoring and threshold

The criteria, scoring and threshold are described in the IMI2 Evaluation Criteria, with the following exception:

IMI2-2014-01-01 IMI2-2014-01-02	If a proposal fails to achieve the threshold for a criterion, the evaluation of the proposal will be stopped.

Evaluation procedure

The full evaluation procedure is described in the IMI2 Manual for submission, evaluation and grant award.

The procedure for setting priority order for proposals with the same score is given in the IMI2 Evaluation Criteria.

The applicant consortium of the highest ranked proposal (stage 1) for each topic will be invited to discuss with the relevant industry consortium the feasibility of jointly developing a full proposal (stage 2).

The applicant consortia of the second and third-ranked proposal (stage 1) for each topic may be invited for preliminary discussions with the industry consortium if the preliminary discussions with the higher ranked proposal and the industry consortium fail. Such contacts should be done in priority order, i.e. the second ranked proposal should be contacted only after failure of pre-discussions with the first ranked, and the third after the second ranked.

Indicative timetable for evaluation and grant agreement

	Information on the outcome of the evaluation (first stage)	Information on the outcome of the evaluation (second stage)	Indicative date for the signing of grant agreements
IMI2-2014-01-01 IMI2-2014-01-02	Maximum 5 months from the date of submission to the first stage.	Maximum 5 months from the date of submission to the second stage.	Maximum 3 months from the date of informing the applicants following the second stage evaluation.

Consortium agreements

In line with the Rules for Participation and Dissemination applicable to IMI2 actions[7] and the IMI2 model grant agreement, participants in Research and Innovation actions are required to conclude a consortium agreement prior to grant agreement.

Submission Tool

Please note: The IMI electronic submission tool **SOFIA** (Submission OF Information Application) is to be used for submitting a short outline proposal in response to a topic of the IMI2 Call 1; no other means of submission will be accepted. SOFIA will be opened for submission of proposals on 9 July 2014. Updates of the proposals may be submitted online until the Call submission deadline. Only the most recent version shall be considered for the evaluation procedure (including eligibility check).

To access the IMI electronic submission tool SOFIA, applicant consortia wishing to submit a short outline proposal will need to complete a request for access to the tool.

[7] Regulation (EU) No 1290/2013 of 11 December 2013 and Commission Delegated Regulation (EU) No 622/2014 of 14 February 2014.