European Cooperation in the field of Scientific and Technical Research - COST -

Brussels, 21 November 2012

BM1207

MEMORANDUM OF UNDERSTANDING

Subject :	Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action BM1207: Networking towards clinical application of antisense-mediated exon skipping

Delegations will find attached the Memorandum of Understanding for COST Action as approved by the COST Committee of Senior Officials (CSO) at its 186th meeting on 20 - 21 November 2012.

MEMORANDUM OF UNDERSTANDING
For the implementation of a European Concerted Research Action designated as

COST Action BM1207
NETWORKING TOWARDS CLINICAL APPLICATION OF ANTISENSE-MEDIATED EXON SKIPPING

The Parties to this Memorandum of Understanding, declaring their common intention to participate in the concerted Action referred to above and described in the technical Annex to the Memorandum, have reached the following understanding:

1. The Action will be carried out in accordance with the provisions of document COST 4154/11 "Rules and Procedures for Implementing COST Actions", or in any new document amending or replacing it, the contents of which the Parties are fully aware of.

2. The main objective of the Action is to accelerate the clinical development of antisense-mediated exon skipping for rare diseases, with a focus on Duchenne muscular dystrophy.

3. The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EUR 20 million in 2012 prices.

4. The Memorandum of Understanding will take effect on being accepted by at least five Parties.

5. The Memorandum of Understanding will remain in force for a period of 4 years, calculated from the date of the first meeting of the Management Committee, unless the duration of the Action is modified according to the provisions of Chapter V of the document referred to in Point 1 above.

A. ABSTRACT AND KEYWORDS

This COST Action aims to advance the development of antisense-mediated exon skipping for rare diseases, focusing on Duchenne muscular dystrophy for which this approach is currently assessed in phase 3 clinical trials. Several challenges hamper its development to wide clinical application: 1) There is no standardized protocol for important biological outcome measures, such as dystrophin restoration. 2) The approach is mutation specific; development for patient subgroups is challenging as most mutations are rare. 3) Fragmentation: several European groups work on preclinical optimization. 4) There is therapeutic misconception amongst patients and unrealistic expectations. This COST Action will address the described issues through 1) meetings and training to standardize outcome measures, 2) meetings with regulatory authorities to discuss alternatives to develop this approach for small patients groups, 3) networking workshops where unpublished data are shared confidentially between parties to foster synergistic work and avoid duplication, 4) training of young scientists in unbiased and clear communication to patients.
Networking is crucial for research in the orphan disease field and this model is applicable to other rare diseases for which exon skipping is currently in preclinical development. Groups involved are anticipated to join the Action when their research moves towards the clinical trial phase.
A.2 Keywords: Personalized medicine, rare diseases, Duchenne muscular dystrophy, antisense oligonucleotide-mediated exon skipping, therapeutic misconception

B. BACKGROUND

B.1 General background

Rare diseases (RD) are defined by the European Commission as “life-threatening or chronically debilitating diseases, with a prevalence of 1 in 2000 or lower”. In fact the term ‘rare’ is misleading, because there are between 5000-7000 rare diseases affecting an estimated 6-8% of the European population. Due to limited patient populations, networking and collaboration are crucial when studying individual RDs. Until recently, research for RDs was mostly done by academic experts, although, currently there is a growing interest of industrialists in developing therapies for RDs (e.g. exemplified by the initiation of RD units by GSK and Pfizer). Nevertheless, translational research for the RD field has unique challenges and hurdles, while expertise is limited and regulations in place have generally been created with common diseases in mind. This is exemplified by the clinical development of antisense-mediated exon skipping for Duchenne muscular dystrophy

(DMD), a severe, inherited neuromuscular disorder (1 in 3500 new-born males), and leading to progressive loss of muscle, severe debilitation and premature death in the 2-4th decade. Treatment is symptomatic and the impact on DMD patients and their families, who have to provide care 24/7 in later stages, is one of the heaviest for a human condition. The disease is caused by mutations in the dystrophin gene that disrupt the genetic code and abolish production of this crucial muscle protein. Antisense-mediated exon skipping is the most promising therapeutic approach and is being tested in phase 3 clinical trials (coordinated by Industry). The aim is to restore the genetic code of the dystrophin gene using antisense oligonucleotides (AO, small pieces of modified RNA). This allows the production of smaller, but largely functional dystrophin proteins also found in less severe Becker muscular dystrophy patients. Lacking a cure, the exon skipping approach aims to convert a severe disease into a milder form, which would improve the quality of life of patients and caretakers.

A number of challenges are hampering the development of this approach to clinical application: *1) Lack of consensus on biochemical outcomes.* The outcome measure used in clinical trials is levels of dystrophin in muscle (primary biochemical outcome measure). However, dystrophin is a challenging protein to quantify. There are no standardized procedures making comparison of (pre)clinical results between academic groups and industry challenging if not impossible. Additional, less invasive surrogate markers (e.g. serum biomarkers) are needed to allow therapeutic monitoring over time. *2) New regulatory models are needed.* The exon skipping approach is mutation specific. The largest group of DMD patients (13%) would benefit from skipping of exon 51, which is currently tested in clinical trials. However, AO targeting other exons should be developed as well to make this approach beneficial for as many DMD patients as possible. Now, each AO is considered a new drug and must go through all phases of clinical development. This will become untenable due to cost, and for the majority of exons patient numbers are too small for conducting trials. *3) Cross-group integration.* DMD is a RD, so a concerted effort is required to further develop and optimize therapies. Multiple groups in Europe are working on AO and/or DMD. Their efforts should be streamlined and harmonized to facilitate development and to jointly tackle the challenges and solve the unknowns. *4) Stakeholder communication.* There is therapeutic misconception in this field. Patients and parents often are not aware of the difference between clinical trials and treatment, and have too high expectations of potential new treatments. This is in part due to the biased way scientists present data.

COST is the best mechanism to address these issues, rather than ESF, ESA, EUREKA! or the Framework Programme. The issues cannot be solved by research oriented networks of academic and/or industry (Framework Programme and EUREKA!). Rather, the issues described require close

and long term networking of all key stakeholders (academia, industry, patients and regulatory agencies). Given that the focus is on a therapeutic approach in development, the unique flexibility offered by COST of adding various COST countries and discussion topics is highly desirable. Finally, it is anticipated that more trials testing the therapeutic potential antisense-mediated splicing modulation will initiate during the COST Action (e.g. for spinal muscular atrophy and myotonic dystrophy). COST allows potential new parties to benefit from the networking done for DMD. Once this COST Action has addressed the abovementioned challenges, this will advance the development of antisense-mediated approaches for RD. Due to the focus of this Action, the most immediate benefits will be for DMD patients and their families, but given the anticipated improved functionality of patients and improved contribution to society of patients and their families this will indirectly benefit society as a whole. Furthermore, it will accelerate the clinical development path for AO-mediated approaches for other RDs, by serving as a model to advance approaches from preclinical to clinical experiment through networking efforts and by addressing current regulatory hurdles.

B.2 Current state of knowledge

AO-mediated exon skipping has been developed over the past 15 years. Proof of concept was first obtained in cultured cells derived from patients and animal models. In these cells dystrophin expression was restored after AO treatment. Animal models were crucial to show dystrophin restoration after local intramuscular and systemic AO treatment. Clinical development focuses primarily on exon 51 skipping (applicable to the largest group of DMD patients). The first two clinical trials were done in the Netherlands and the UK, showing local dystrophin restoration after intramuscular AO injection without side effects. Follow up trials in Belgium, Sweden and the UK confirmed dystrophin restoration after intravenous and subcutaneous AO treatment. The open label extension trial following one of the systemic trials has now been on-going for close to 3 years. Currently, multiple trials are on-going globally for exon 51 skipping, including a pivotal double blind, placebo-controlled phase 3 trial. Additional trials for other exons are on-going (exon 44 skipping, applicable to 6% of patients) or planned (exon 45 skipping, exon 53 skipping, each applicable to 8% of patients) in Europe. The exon skipping approach for DMD has been pioneered in Europe, Japan and Australia. Europe has taken a clear leadership role in the clinical development of this approach: much of the current preclinical work takes place in laboratories of European experts (for which Action members receive Framework Programme funding) and the first 5 clinical trials took place in Europe (mainly funded by industry). The European leadership role has been

fostered by the Framework Programme 6 funded TREAT-NMD (Translational Research in Europe to Accelerate Treatment for Neuromuscular Disorders) Network of Excellence. The aim of this network was harmonization and preparation for upcoming clinical trials, e.g. through generating patient and trial site registries and standardizing care. The network also aimed to facilitate collaboration and harmonization of on-going research projects. In the exon skipping field, preliminary meetings funded by TREAT-NMD to jointly discuss common hurdles at the pre-competitive level in a confidential setting have been held by some of the members from COST countries. This model worked extremely well, but without funding, the follow up to these initial meetings, though much needed, is difficult. This COST Action will involve a regular follow up of these initial meetings discussing a variety of topics to streamline research, facilitate collaboration and further the leadership role of Europe in the (pre)clinical development of AO-mediated exon skipping. The COST Action will also address regulatory hurdles currently hampering clinical development of AO-mediated exon skipping for RDs.

B.3 Reasons for the Action

There is currently no funding for networking, impeding researchers from jointly tackling these issues, as this requires meetings on a regular basis. COST would provide the means to fully integrate and complete these efforts. This COST Action is mainly aimed at science/technological advance, but due to the translational nature and benefits to patients, there is also a clear impact on economic/societal needs. DMD is a RD with an incidence that is the same worldwide. As such, hurdles for clinical development have a global impact and can only be solved by global commitment of all key stakeholders. Due to the pioneering position of Europe, the majority of these stakeholders reside in Europe. Ideally, a mechanism should have been in place for wide application of AO-mediated exon skipping. As this is an innovative approach, and translational research in the RD field has only just initiated, systems are not yet optimal. Due to the progressive nature of DMD, it is essential that hurdles currently hampering the clinical application of this approach are solved as quickly as possible. This will benefit the DMD patients eligible for exon skipping (~80% of all patients), but will also provide infrastructure to facilitate and accelerate AO-mediated treatments for other rare diseases. Notably, most RDs are caused by genetic mutations and many of these are well suited for the personalized medicine type approach of AO-mediated exon skipping.
Objectives/Methods and Expected Results: (1) Stakeholder meetings for dystrophin quantification will yield standardized procedures for dystrophin quantification and rotation of trained personnel will allow implementation in laboratories in Europe. (2) To set up new regulatory models to

develop personalized medicine type approaches, this Action involves stakeholder meetings with the European Medicine Agency and Food and Drug Administration to educate regulators on the need to develop innovative trial designed for rare diseases. (3) This COST Action aims at fostering synergy through small workshops (2-3 per year) to confidentially discuss recent findings and common problems. Dissemination is done through a large meeting for key stakeholders working on AO therapeutics. The workshops will generate opinion papers; the large meeting allows dissemination and identification of additional Parties for this Action. (4) Therapeutic misconception will be addressed through interactive training workshops involving young scientists. This will lead to scientists better able to communicate clearly with patients to avoid false hope or incomprehensible scientific presentations to a patient/lay audience.

B.4 Complementarity with other research programmes

This Action paves the way for clinical AO development for DMD and other RDs, working towards the International Rare Disease research Consortium (IRDiRC) goal of having 200 treatments for RDs in 2020. The parties proposed for this COST Action have a strong track-record in initiating consensus panels to address the issues (e.g. Clinical Outcomes International Consensus, and MDEX (Muscular Dystrophy Exon Skipping Consortium). Preliminary meetings have been held through pilot funding, supported in part by small stakeholder foundations, an European infrastructure grant (TREAT-NMD). The research of this COST Action participants is funded through Framework Programme 7 (e.g. BIO-NMD, NEUROMICS, RD-CONNECT). The aim of this COST Action will be to provide the networking infrastructure to coordinate the research funded by these grants and prevent duplication of effort and jointly address common bottlenecks.

C. OBJECTIVES AND BENEFITS

C.1 Aim

The aim of the Action is to accelerate the clinical development of antisense-mediated exon skipping for rare diseases, with a focus on Duchenne muscular dystrophy.

C.2 Objectives

(1) Consensus on biological outcome measures: there is currently no standardized procedure to quantify dystrophin levels in (pre)clinical samples and surrogate markers are lacking. This hampers

(pre)clinical development as comparison between groups or trials is not possible and therapeutic monitoring over time in patients is difficult. *Deliverables*: 1.1: Standardized protocols for dystrophin quantification; 1.2: Trained personnel to conduct the procedure; 1.3: Consensus on surrogate markers (serum biomarkers)

(2) New regulatory models for AO-mediated treatments in RDs: the parties involved in this Action have previously organized preliminary workshops on exon skipping with the European Medicine Agency (EMA) (40 participants) and the Food and Drug Administration (FDA) (75 participants). Both stressed the importance of international consensus on the topics presented here, as this is crucial to expedite exon skipping therapeutics for DMD and other RDs. Further meetings will be organised to discuss new regulatory models. *Deliverables***:** 2.1: A meeting with the EMA involving academics, clinicians, industry and patients; 2.2: A meeting with the FDA involving academics, clinicians, industry and patients

(3) Foster synergistic work: the COST Action will organize 2-3 small workshops per year with representatives from each party to a) confidentially present recent findings to consolidate efforts b) discuss common problems and issues currently hampering development and optimization of this approach. This will be disseminated and discussion further at a large key stakeholder meeting. *Deliverables*: 3.1: At least ten workshops; 3.2: A large meeting open to all key stakeholders; 3.3: At least 2 joint opinion papers on topics discussed at the workshops

(4) Tackle therapeutic misconception: young scientists will be trained in an interactive workshop on how to present their data to lay people (patients) in a responsible and clear way. *Deliverables*: 4.1: One (or more) training workshop for young scientists to train their skills in communication of scientific results to patients and their families; 4.2: Additional educational meetings with clinicians and patients to disseminate the AO work.

C.3 How networking within the Action will yield the objectives?

(1) Biological outcome measure consensus: A specific Working Group containing dystrophin experts from COST and Non COST institutions will coordinate this objective. This Working Group (WG) has already organized a preliminary consensus meeting. Standardized protocols for dystrophin quantification will be achieved through 2 meetings with participants from academia, industry and patients groups to evaluate and discuss different methods and come to a common, standardized methodology. Personnel conducting the dystrophin quantification will be trained through rotations to specific sites to allow implementation of the standardized methodology in their

own laboratory. The same model will be applied to potential surrogate makers once sufficient preliminary work confirms their potential. *(2) New regulatory models*: Meetings with FDA and EMA will be organized by a dedicated Working Group consisting of members involved in organizing previous preliminary meetings. This COST Action involves follow up meetings with both organizations to present new results, and discuss alternative pathways for AO development of additional exons, and will involve regulators, academics, clinicians, and industry and patient representatives. *(3) Foster synergistic work*: A) The small workshops will be organized by the COST members involved in this Action, who will also select topics. External experts will be invited if needed. Topics can be added or prioritized when needed. B) To allow dissemination of the work and facilitate discussion a large meeting will be organized for all key stakeholders working on AO therapeutics (Academia, Industry, Patients, and Regulators). Young scientists will be encouraged to participate and contribute. *(4) Tackle therapeutic misconception*: Young scientists will be trained in an interactive workshop on how to present their data to lay people (patients) in a responsible and clear way. They will receive feedback from expert presenters and representatives from patient organizations. The workshop will be set up through a Working Group containing also representatives from parties and patient organizations. Together with Framework Programme networks in the RD field, this WG will organize educational meetings for clinicians and patients to disseminate the state of the art of the AO work.

C.4 Potential impact of the Action

(1) Biological outcome measure consensus: Standardized protocols will facilitate (pre)clinical development of exon skipping and allow comparison between labs and all trials aiming for dystrophin restoration. *(2) New regulatory models*: A quicker development path for new AO will accelerate the clinical application of additional AO for DMD and other RDs. This will pave the way for clinical AO development for even rarer diseases, working towards the IRDiRC goal of having 200 treatments for RD in 2020. *(3) Foster synergistic work and reduce fragmentation*: The workshops will foster networking between groups in Europe working on exon skipping to consolidate the leading role that Europe has in developing this approach for DMD and other RDs. The workshops will allow a concerted effort to further the field with less funding (as there is no duplication of efforts) and will improve networking in the exon skipping field. *(4) Tackle therapeutic misconception*: Trained scientists who are able to communicate better with patients to provide information, and work with patient organizations in the development process of therapeutic approaches.

C.5 Target groups/end users

Main end users are RD patients for whom AO-mediated approaches are in development and clinicians treating them. However, academics and industry working on AO-mediated approaches in the RD field would also be able to exploit the expertise obtained by this Action accelerate the development of therapeutic approach.

D. SCIENTIFIC PROGRAMME

D.1 Scientific focus

Objective 1: Biochemical outcome consensus: AO-mediated exon skipping for DMD aims at restoration of the dystrophin protein in skeletal muscle. As such, dystrophin levels observed in muscles after treatment in preclinical animal experiments and clinical trials are the most important biochemical outcome measure. This can be achieved by quantification of fluorescent signals after immune-histochemical staining of muscle cross sections, which provide information on the percentage of dystrophin positive fibres, proper location of dystrophin and relative levels. Complementary, western blotting provides quantitative and qualitative information on dystrophin (i.e. dystrophin levels and size) in muscle tissues. Dystrophin is a challenging protein to quantify, due to its low abundance (0.002% of total muscle protein) and size (427 kDA). Currently, methods to do this are not standardized and different laboratories use different protocols to assess dystrophin levels, use different types of controls for references etc. This makes comparison between laboratories or trials impossible, thus impeding the optimization and implementation of AO-mediated exon skipping for DMD.
In 2010 a preliminary study was done using funding from a Framework Programme 6 funded Network of Excellence. Muscle samples from Becker muscular dystrophin patients (with known low levels of shorter dystrophins) were distributed to academic and industrial expert laboratories, which assessed dystrophin levels in these samples by immuno-histochemical staining and western blot analysis. A consensus meeting was held in September 2010, but unfortunately due to limited quality of the very old muscle samples and the lack of control healthy muscle, it was not possible to decide on the most optimal method. Nevertheless some methods were clearly more suited than others, allowing for already more focused future meetings. Due to lack of funding, no further work has been conducted towards harmonizing the biochemical outcome measure to date.

In the future hopefully less invasive methods can be used to monitor treatment effects, e.g. using serum biomarkers. *Scientific Workplan*: To standardize outcome measures, consensus has to be reached on what is the most sensitive protocol to assess dystrophin levels by histochemical analysis and western blotting. To allow good comparison muscle samples from patients with lower levels of dystrophin (Becker muscular dystrophy patients) will be blinded and send out to expert groups (at least 4 institutions from COST countries, 1-2 in non-COST Institutions). Here, experienced personnel will conduct the dystrophin level quantification using protocols operational in that group. Dystrophin levels related to the control muscle tissue also provided to each group. During a first consensus meeting results will be presented to the parties involved (~30-40 people) and the 2 most optimal protocols for western blotting and histochemical analysis will be selected by those involved. These will then be implemented in each expert group and compared head to head during a second tier analysis, again involving blinded samples from Becker muscular dystrophy patients. During a second consensus meeting (involving the same parties, as well as additional people if needed) the results will be presented, including what the expert groups perceived as the advantages and disadvantages of each method. During this meeting, and based on the reliability, reproducibility and assessment of the approaches by expert groups, one standardized method is selected for histochemical analysis and western blotting. This will be accompanied by a methods publication in a scientific journal. To facilitate implementation of the selected methods, the COST Action will develop training rotation visits to expert group. At the early stage this will be the expert groups visiting each other (involving ~5-10 people rotating and ~5 people involved in hosting the visitors), but at later stages it will involve visits of additional scientists working in this area to expert groups. The same model will be employed to set up standardized procedures for measuring serum biomarkers once these have been identified (one or two tier process depending on the complexity of the measurements).

Objective 2: New regulatory models: AO-mediated exon skipping is a personalized medicine type of approach. For DMD, on-going clinical trials focus on exon 51 skipping, which applies to the largest group (13% of patients). Ideally, AO targeting other exons are developed as well to fully exploit this approach for DMD, and make it beneficial for as many patients as possible. Furthermore, AO targeting exons in other genes are in preclinical developed for other RDs. The current regulatory models were generated with common diseases in mind and are not well adapted to personalized medicine type approaches and/or approaches targeting RDs. E.g. each AO is considered a new drug by the regulatory agencies, meaning it has to go through all phases of clinical development. This currently hampers the development of AO targeting exons benefiting small groups of DMD patients, as well as other AO for other RDs (DMD is one of the most

"common" RDs) as trials are untenable due to limited patient numbers and costs.
Scientific Workplan: It will be crucial to educate regulatory agencies in the specific hurdles and challenges of treatment development for RDs and/or using personalized medicine approaches, as expertise with this background is limited. Two preliminary workshops have been organized in the past with the European Medicine Agency (EMA, 2009) and the Food and Drug Administration (FDA, 2010). This COST Action will organise follow up meetings with both organizations where all key stakeholders will participate in these meetings (regulators, academics, clinicians, industry and patient representatives, ~40-70 attendees per meeting). If needed and depending on the clinical trial development for DMD and the preclinical development in other RDs, additional meetings will be organised.
Objective 3: Cross-group integration: Multiple groups in Europe are currently working on AO for DMD (~10 groups, involving ~100 scientists) and/or other RDs (~20 groups). This work is funded through Framework Programme 7 grants, national grants from the government and grants from patient organizations. For DMD the work focuses on optimization of delivery by modifying AO or using delivery vehicles or conjugates, optimizing dosing and regimen schedules in animal models for AO chemistries currently tested in trials, identification of surrogate biomarkers to monitor disease progression and therapeutic benefit, natural history studies in DMD and Becker muscular dystrophy patients amongst others. The efforts should be streamlined, to prevent overlaps in work being done. Furthermore, while generally these groups have different perspectives and "niches", there are common hurdles and challenges that should be tackled jointly.
Scientific Workplan: This COST Action will involve 2-3 small workshops per year. Workshops will be kept relatively small (maximum of 20-25 people, generally limited to 1-2 representatives per Party) to facilitate discussion. Topics will be selected by the parties involved. These can be AO specific (e.g. toxicity or delivery), DMD specific (e.g. surrogate outcome measures, dystrophin levels needed for patient benefit) or address issues specific for other RDs for which AO treatment is in development (envisaged in later stages of this COST Action). The combined expertise of these parties and the expertise generated by the COST Action will be further disseminated to all interested parties in a large meeting (involving ~200-400 key stakeholders from academia, industry, patient organizations, government and regulatory agencies, the majority from COST countries). ESRs will be explicitly encouraged to participate in the meeting through fellowships.
Objective 4: Stakeholder communication: There is therapeutic misconception in this disease field. Patients and parents often are not aware of the difference between clinical trials (an experiment done in humans with a compound for which efficacy and safety is yet uncertain) and a treatment, and have too high expectations of potential new treatments. This is in part due to the biased way

data is presented by scientists, who have been taught how to present to scientists, but not how to present to patients and parents.
Scientific Workplan: The COST Action will develop an interactive workshop on how to present data to patients in a responsible way. Each workshop will involve a maximum of 10 participants, representatives from patient organizations (~2-4) and expert presenters to patients from parties of COST Institutions (~1-2). Furthermore, together with scientific communities from Framework Programme focusing on rare diseases the Action will develop educational meetings to clinicians and patients to disseminate the current state of the art.

D.2 Scientific work plan methods and means

Objective 1: Biochemical outcome consensus: The work planned towards this objective will be coordinated by the Biochemical Outcome Measurements (BOM) WG, which will consist of at least 3 parties involved in the previous consensus meeting, assisted by international experts from academia and industry (the majority from COST). The BOM WG will coordinate the distribution of muscle samples to the expert groups during year 1 of this COST Action. The BO WG will organize the first consensus meeting in year 2 (month 13-15) to identify the two most promising procedures for both immune-histochemical analysis and western blotting. During the second tier comparison the BOM WG will organize distribution of new muscle samples to expert groups for head to head comparison of the two selected methods for immune-histochemical and western blot analyses. The BOM WG will organize the second consensus meeting (end of year 3) to select the most optimal procedures for the two methods. The BOM WG will coordinate the writing of standardized operating procedures and scientific methods papers by one of the parties (coordinating party) selected during the second consensus meeting, as well as the editing by each of the expert Parties and a final edit by the coordinating party. These protocols will be made available on the internet (year 4) and a methods paper will be published in a scientific journal. The BOM WG will also coordinate rotation visits of experts to expert groups during tier 2 testing and of interested groups working on dystrophin quantification in year 4.
The BOM WG will coordinate the standardization of serum biomarkers as well. It is anticipated measuring these will be less challenging, so likely a one round consensus process will suffice. If needed, the BOM WG will recruit 1 or 2 additional members with expertise in serum biomarkers to facilitate coordination and collection and distribution of serum samples.
Objective 2: New regulatory models: The regulatory model (RM) WG will consist of parties also

involved in coordinating previous meetings with EMA an FDA. The RM WG will coordinate the organization of follow up meetings with both organizations (Year 2 and 3) to present new results and discuss alternative, innovative trials set ups and regulatory paths for AO development of additional exons. They will also coordinate the writing of briefing documents by all parties to distribute to EMA and FDA ahead of the meeting. The briefing document will be based on the document previously used at the EMA meeting and updated where needed. Depending on the preclinical development in other RDs, Parties from those areas can join the RM WG and plan additional meetings.

Objective 3: Cross-group integration: The Parties of this COST Action of COST Institutions will organize 2-3 small workshops per year, where participants can confidentially present unpublished work. Topics will be selected by the parties. Meetings will be scheduled on an afternoon and a morning, to allow for a workshop dinner with all participants to increase networking and collaboration. When a certain topic discussed is of broader interest, a selected party will coordinate the generation of a statement paper by all parties to disseminate the opinion to the general public/scientific field.

The Meeting on Antisense-mediated Therapeutics (MAT) WG will coordinate the organization of a large meeting in year 3 of the COST Action. This is anticipated to facilitate recruitment of new members in year 4. The MAT WG will manage the scientific content of the meeting. The meeting will be held jointly with Framework Programme 7 funded networks on RDs to allow maximum impact and reduce costs.

Objective 4: Stakeholder communication: The Stakeholder Communication (SC) WG consists of representatives from 2 parties with extensive networks in the patient community, who are expert presenters at patient/parent meetings. The SC WG will be assisted by patient organization representatives. The SC WG will organize an interactive workshop on how to present data to patients in a responsible way in Year 2. Participants will present their own work at lay audience level and will receive feedback from expert presenters to patients and representatives from patient organizations. The workshop will be kept small to allow interaction (maximum 10 participants) and is mainly aimed at early stage researchers working in the rare diseases field, although it will be open to all researchers. In case of oversubscription, participants will be asked to explain what they hope to learn during the workshop and motivate why they want to participate and the SC WG will select the 10 best. The workshop will be evaluated and feedback will be used to organize another workshop in Year 3. Depending on the interest of participants more workshops can be added.

Educational meetings will be set up by the SC WG in collaboration with representatives Framework Programme 7 funded networks on RDs (most parties of this COST Action are involved

in several consortia from Framework Programme 7).

E. ORGANISATION

E.1 Coordination and organisation

This COST Action will have a Management Committee (MC) consisting of 8 parties from 5 institutions and 1-2 representatives from patient organisations. The Applicant will chair MC meetings, which are linked to objective 3.1 workshops that take place 2-3 times per year. The MC will discuss management issues, the focus of the Action (relevance and timeliness) and plan future workshops and meetings. The perspective of patient representatives will actively be sought to ensure the objectives of this Action align with their needs. When needed, teleconferences or ad hoc meetings will be arranged. MC will only take place when >50% of the members are present. A website dedicated to this COST Action will be generated and maintained by a party maintaining websites for large Framework Programme funded networks, to which the COST Action website will be linked. The website will contain information on the aim and objectives of the Action and on meetings and workshops organised. The website will also contain non-confidential minutes of meetings and workshops and products generated by the Action (e.g. opinion papers and protocols). A dedicated password protected section of the website will be set up with different levels of access to allow sharing of documents between WG members and MC members. At least every 6 months, chairs of the WG and the coordinator of the Action will provide brief updates on objectives to be put on the website.

This COST Action aims to accelerate development of AO-mediated therapies for RDs through international networking. Funding to conduct research is in place through grants from Framework Programme, government and patient organizations. This COST Action will streamline this work through small workshops, organized by the coordinator on topics agreed upon by the MC. For other objectives, dedicated WG will be appointed. In objectives 1, 2 and 3.2 representatives from Non-COST institutions will participate (for objectives 2 and 3.2 representatives will be involved during the Action). Participation of these representatives will be provided by stakeholder foundations or local non-COST institutions. Training of personnel will be done towards objective 1 to implement standardized operating procedures. In addition, researchers can be rotated between parties to share techniques. Workshops organized for objective 3.1 facilitate identification of eligible parties to rotate and to host. Rotations have to be approved by the majority of the MC.

Milestones of this COST Action: 0.1 COST Action website online (M3); 1.1 Standardized operating

procedures for dystrophin quantification published on website (M48); 2.1 Briefing document for EMA and FDA meetings published on website (M36); 2.2 Report on EMA meeting published on website (M28); 2.3 Report on FDA meeting published on website (M40); 3.1 Report on the meeting on AO-mediated treatments published on website (M42); 3.2 Publication of at least 2 statement papers (M48); 4.1 Report on the evaluation of the first stakeholder workshop (M32); Additional milestones are likely to arise during the COST Action.

E.2 Working Groups

WGs will coordinate the work done towards objective 1 (Biochemical Outcome Measurements), objective 2 (Regulatory Models), objective 3B (Meeting on Antisense Therapeutics) and objective 4 (Stakeholder Communication). WGs will consist of relevant representatives of parties involved (see D2). The MAT WG will work with representatives of Framework Programme 7 projects to jointly set up a meeting. WGs will select a Chair who will report to the MC every 3 months (or more often when deemed necessary by the WGs or the MC) through email, teleconference or during face to face meetings. When needed, joint WG and MC team meetings will be organized.

E.3 Liaison and interaction with other research programmes

Parties involved in this COST Action are also involved in numerous Framework Programme funded research projects and networks. Most notably the RD-Connect and NEUROMICS projects, which will start in November and October 2012, respectively, and focus on RDs. The TREAT-NMD Network of Excellence is no longer funded by Framework Programme, but has been sustained. Other projects focusing on AO-mediated treatments are currently in the negotiation stage. The efforts and achievements of this COST Action will be disseminated during management meetings of the relevant Framework Programme funded projects by parties involved in both. If needed, liaising with relevant projects can be facilitated by the TREAT-NMD and RD-Connect infrastructures. The meetings planned by this COST Action will be disseminated to these networks and joint meetings will be planned. For educational meetings for patients this COST Action can link to the EUPATI network. Parties involved in the Framework Programme funded projects focusing on AO-mediated treatment of RDs currently not involved in this COST Action will likely become involved and participate in workshops and meetings organized for objective 3 and will supply

additional researchers for the workshop organized towards objective 4. When needed, additional joint meetings or workshops can be organized. As RDs, such as DMD, affect patients globally, solving the hurdles requires a global effort. As such, non-COST countries will be involved in objective 1, 2 and 3. It is not envisaged that this networking COST Action will generate intellectual property (IP). Nevertheless an IP sharing committee, consisting of a representative of each party from COST Institutions will be put in place and the MC will assess whether potential IP has been generated during each MC meeting. Notably, due to the translational nature of the topic, parties all have expertise with IP and are well suited to identify potential IP.

E.4 Gender balance and involvement of early-stage researchers

The Applicant is a board member in a network that strives at gender equality of her Institute and will ensure gender equality in this COST Action. The ESRs will be involved in objectives 1, 3 and 4, working towards training the next generation translational scientists.

F. TIMETABLE

This COST Action will last 4 years.
Timetable Objective 1 (Biochemical outcome consensus): Year 1: Distribution and analysis of muscle samples by expert parties and preparation of first consensus meeting; Year 2: First consensus meeting and rotation of personnel between expert parties; Year 2-3: Distribution and analysis of second tier muscle samples and preparation for second consensus meeting; Year 4: Training rotations at expert parties and generation of standardized protocols for dystrophin quantification and method paper on protocols; Year 1-4: Applying a one and/or two tier model for additional biological makers identified through the course of this COST Action
Timetable Objective 2 (New regulatory models): Year 1-2: Preparation for meeting with EMA and generation of briefing document; Year 2: EMA meeting and preparation of meeting with FDA; Year 3: Meeting with FDA and report of EMA meeting; Year 4: Report of FDA meeting, (optional) additional meeting with EMA or FDA
Timetable Objective 3 (Cross-group integration): Year 1-4: 2-3 small workshops on selected topics each year, rotation of personnel and statement papers on relevant topics generated; Year 3: Meeting on AO-therapeutics for rare diseases

Timetable Objective 4 (Stakeholder communication): Year 1-2: Preparation for first workshop; Year 2: Workshop, evaluation of workshop, preparation for second workshop; Year 3-4: Second workshop (and optionally more workshops)

G. ECONOMIC DIMENSION

The following COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: FR,IT,NL,SE,UK. On the basis of national estimates, the economic dimension of the activities to be carried out under the Action has been estimated at 20 Million € for the total duration of the Action. This estimate is valid under the assumption that all the countries mentioned above but no other countries will participate in the Action. Any departure from this will change the total cost accordingly.

H. DISSEMINATION PLAN

H.1 Who?

The results of this Action will be disseminated to all relevant stakeholders. These stakeholders will be involved in the Action as much as possible to facilitate dissemination. For objective 1 (outcome measure consensus) the target audiences are Academia and Industry involved in preclinical and clinical work on therapeutic approaches that restore dystrophin. For objective 2 (new regulatory models) the main audience is international and national regulatory bodies, but new models will also benefit other groups working on therapeutics for rare diseases: Academia and Industry and the rare disease patients for which these approaches are being developed. For objective 3 (streamlining of work) the main audience will be academia, but industry, patients and regulators will benefit as well. The aim of objective 4 is to facilitate researchers to present to patients and lay audiences and to educate all key stakeholders.

H.2 What?

For objective 1 the standardized protocols will be published on the website of this COST Action.

The scientific paper will be published in a peer-reviewed journal read by researchers in the Duchenne field (e.g. Neuromuscular Disorders, Muscle Nerve or PLoS Currents Muscular Dystrophy).
For objective 2 the briefing document and meeting reports will be published on the website of this COST Action.
For objective 3 meeting minutes of the workshops are confidential and will be distributed by email to workshop participants. Statement papers on selected topics will be published in relevant scientific journals. Expertise gained by this COST Action will be disseminated through a meeting on AO-mediated therapeutics. The meeting report will be published on the website of this COST Action and will be held jointly with Framework Programme networks on rare diseases to maximize impact.
For objective 4 a report on the workshop and its evaluation will be published on the website of this COST Action.
Workshops and meetings planned for this COST Action will be published on the website of this COST Action.
A dedicated COST newsletter will be sent to interested parties (subscription possible on the website of this COST Action) every 6 months.

H.3 How?

The reports and protocols generated by this COST Action will be published on the website of the COST Action (except for the minutes of the Objective 3 workshops, which are confidential). Furthermore, statement papers and methods papers will be published in relevant scientific journals. The large number of Framework Programme funded networks in this area will facilitate dissemination of the results of this COST Action and when possible, links to the information with be placed on websites of other networks (most of which are maintained by the same party). Upon publication of these documents on the website or in journals, their availability will be disseminated to participants involved in that objective by email, and to the larger field through newsletters of networks in the field (e.g. TREAT-NMD, RD-Connect, newsletters of patient organizations and the newsletter of this COST Action).
The workshops and meetings of this COST Action and the possibility for training in standardized dystrophin quantification protocols will also be mentioned in newsletters and listed on websites of research networks in the rare disease field.
The newsletter of this COST Action will be instrumental to provide 6 monthly updates on the

activities of the network to interested parties. When needed, additional newsletters can be sent, e.g. when major milestones have been achieved. The possibility to subscribe to the newsletter will be mentioned on websites and in newsletters of research and patient networks.
The MC will discuss the status of the dissemination on a yearly basis and adapt the strategy when needed (e.g. when a new research network is formed, when additional parties become involved in the COST Action, or when new objectives are added during the course of the Action).