Executive Summary for the COST Action BM1207/SCOPE-DMD stakeholder meeting hosted by the European Medicine Agency on

Antisense oligonucleotide-mediated exon skipping therapy development for Duchenne muscular dystrophy (DMD)

April 29 2015, London UK

Purpose of the meeting

This workshop is a follow-up to a seminal workshop EMA hosted in 2009 to discuss antisense oligonucleotide (AON) therapy development for Duchenne muscular dystrophy (DMD). During the past 6 years, new data has been generated in clinical trials on exon skipping using different compounds, efforts on outcome measure development have come to fruition and much natural history data has been collected. Therefore it is timely to **exchange knowledge and perspectives** in an open forum with all stakeholders (patient representatives, academics, regulators and industry), with the ultimate aim to **streamline and accelerate therapy development for DMD**.

Duchenne muscular dystrophy

Duchenne muscular dystrophy is a severe, progressive muscle disease affecting 1 in 5000 male births. The disease is characterized by continuous and irreversible loss of muscle tissue and function. Affected children are typically diagnosed at about four or five years of age, when it becomes apparent that their motor abilities are restricted, (e.g. repeated falling, difficulty with running and trouble climbing stairs). Without treatment most require the use of a wheelchair around the age of 9.5 years. Orthopaedic problems resulting from extreme muscle weakness, respiratory and cardiac complications emerge and death often occurs by the late teens or early adulthood, mostly due to respiratory or cardiac failure. With optimal care, including assisted ventilation patients can survive three decades, but older patients have profound weakness and require assistance with all activities of daily life, with a high emotional and financial burden to patients, families and society.

An innovative approach to DMD therapy: exon skipping

The exon skipping approach addresses the underlying cause of DMD, i.e. lack of functional dystrophin protein in muscle. Antisense oligonucleotides (AONs), which are modified pieces of DNA or RNA, allow the production of partially functional dystrophin proteins by re-establishing the open reading frame in the mutated dystrophin transcripts. Currently two different chemical modifications are being tested in clinical trials and more are undergoing pre-clinical evaluation. Exon skipping is a compelling example of a personalized/precision medicine approach, since the exon to be targeted depends on the individual mutation of the patient. While certain sizable groups of individuals would benefit from a single AON, the majority of AONs apply to smaller groups, each making up less than 2% of all patients. This poses scientific as well as regulatory and ethical challenges to exon skipping development:

- How to prioritize
- Who prioritizes?
- How to assess efficacy in small groups of patients
- Who is interested in developing AONs for small groups of patients?
- Should it be established that skipping a certain exon leads to clinical benefit, is it then ethical to test AONs targeting additional exons in placebo-controlled trials?

These are only some of the pressing questions that have emerged on the developmental pathway of AON therapy that imply the need for a collective thinking approach to provide satisfactory answers.

DMD individuals and their families: expectations from therapies

Individuals affected by DMD and their families are aware of the challenges that need to be faced while attempting to provide effective therapies for this devastating disease. Research has shown that affected individuals and parents would welcome, for the time being, therapies that slow down disease progression, in line with what the therapeutic approaches currently in development aim to achieve. Furthermore, affected individuals and their parents are willing to accept a level of uncertainty inherent to the therapy development pathway and are willing to contribute to it at every step. Finally, patients and parents are keen to give input and advice at an earlier stage of drug development about trial design, choice of

outcome measures, explaining what is clinically meaningful to them, how they see benefit risk, in- and exclusion criteria and on how to collect sufficient data in groups of patients not fitting these criteria in order to enhance the possibilities for extrapolation of trial results to these groups of patients.

Outcome measures & clinical benefit for DMD

During the past 5 years understanding of the natural history of different stages of DMD and its relation to outcome measures has increased enormously.

Outcome measures that show correlation with slowing of disease progression should be appropriate endpoints in clinical trials given the high value patients assign to it. Similarly, outcome measures that predict disease milestones should be acceptable. As a data-supported example, the time it takes to run 10 meters is predictive of when patients will lose ambulation, so a 2 second difference between treated and placebo groups in this test can mean a delay of months or years in the decrease of motor function capabilities.

The DMD field has generated a huge amount of data on the use of outcome measures and their relevance. As a corollary to that, the field is in need of clear and consistent guidance on how the regulators expect the outcome measures to be used in the ambulant population. In addition, the majority of trials are done in a selected group of ambulant patients that represent only a stage of the disease, but very young and older patients also deserve to benefit from therapeutic options made available on the market so guidance on the utility of the emerging outcome measures in these patient groups is also sought.

The need for innovative guidelines for DMD therapy development

The therapy development process for DMD would be greatly facilitated by making available in the public domain up to date guidelines containing a direct input from the regulators. Furthermore, the introduction of novel trial designs that would allow inclusion of patients in different disease stages (e.g. ambulant and non-ambulant), with different mutations (e.g. the smaller groups for mutation specific approaches), and when possible trials without a placebo group, could contribute to a significant leap forward towards the offer of long awaited, sound therapeutic options for DMD patients.

Furthermore, the field asks for alignment and coherence in the scientific advice provided by the regulators (e.g. EMA, FDA) for planning trials. This alignment is not only needed for a single therapy, but also when different therapies are administered at the same time, since it is anticipated that in the future most DMD patients will receive a combination of treatments. Having guidelines on these aspects would be of paramount importance.