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Duchenne Muscular Dystrophy

1 Introduction

This briefing note seeks to ascertain the following in relation to Duchenne Muscular Dystrophy (DMD):

- What are the symptoms of the condition?
- Are there any statistics on survival rates?
- How many people sufferer from DMD in NI, the UK and worldwide?
- What are the current treatment options?
- Is there any on-going research into the condition?

2. Duchenne Muscular Dystrophy

Muscular dystrophy (MD) is a genetic, inherited condition where slow, progressive, muscle wasting leads to increasing weakness and disability. There are many types of genetic muscular disorders, each differing in their symptoms and severity. This briefing note focuses on Duchenne Muscular Dystrophy (DMD), a devastating and aggressive condition. DMD is the most common and most severe type of muscular dystrophy.¹ It is caused by an abnormality (mutation) of the dystrophin gene, found on the X chromosome.² The dystrophin gene is responsible for telling the body how to make the protein dystrophin, which is an essential component for normal muscle function.

¹ NHS website www.cks.nhs.uk/patient_information_leaflet/muscular_dystrophy# Website accessed 27.5.11

² www.patient.co.uk/health/Duchenne-Muscular-Dystrophy.htm Website accessed 27.5.11

Without dystrophin, the muscle cells cannot survive.³ Eventually the muscle cells break down and die.

3. What are the symptoms?

Generally, there are no distinct symptoms of DMD at birth. Reliable genetic and protein tests are available in hospitals to accurately diagnose DMD.⁴

The condition primarily affects boys and does not necessarily progress at the same rate for every child affected. As the child gets older, the muscles become weaker. In the first few years of life, a child with DMD can show signs of weakness in the muscles of the legs, which leads to mobility and movement problems.⁵ Some children with DMD can also have behavioural, developmental or learning difficulties.⁶ In comparison with their peers, motor skills milestones - such as running, hopping, jumping and climbing are delayed. The bones develop abnormally, causing skeletal deformities of the spine and other areas.⁷

When the muscle cells die, the child develops a very obvious gait and falling becomes frequent. This happens just before the ability to walk independently is lost. Eventually, boys with DMD develop a curved spine (known as scoliosis) and rely on the use of a wheelchair from around the ages of 9-12 years of age.⁸ During the teenage years, the arms, chest and neck muscles can also be affected. As the disease progresses, the heart muscle may grow bigger and weaken, and as a result cause problems with the heartbeat.⁹ Likewise, the diaphragm may also weaken and lead to breathing problems. By the late teens or twenties, the condition is severe enough to lead to premature death.¹⁰ In the majority of cases, it is likely that the cause of death results from cardiac or respiratory failure.

4. Are there any statistics on survival rates?

DMD is fatal and there is no cure. However, it is now more likely that patients with DMD will reach adulthood. Compared with historical data, the average life expectancy has improved and is now around 20 to 30 years of age.¹¹ The advent of multidisciplinary and specialist care to manage the symptoms – for example, supporting breathing with a ventilator, cardiac care and the administration of steroids early in childhood has helped to increase survival rates over the last 50 years.

³ www.dfsq.org.uk/understanding-dmd/understanding-dmd/what-is-duchenne-muscular-dystrophy.html

⁴ NHS website www.cks.nhs.uk/patient_information_leaflet/muscular_dystrophy# Website accessed 27.5.11

⁵ Muscular Dystrophy, NHS 24, Health Information and Self-Care Advice for Scotland, Health Library, Muscular Dystrophy, http://www.nhs24.com/content/default.asp?page=s5_4&articleID=257 Website accessed 27.5.11

⁶ Muscular Dystrophy Campaign website: www.muscular-dystrophy.org/about_muscular_dystrophy/conditions/97_duchenne_muscular_dystrophy Website accessed 31.5.11

⁷ National Institutes of Health, available online www.genome.gov/19518854 Website accessed 27.5.11

⁸ NHS website www.cks.nhs.uk/patient_information_leaflet/muscular_dystrophy# Website accessed 27.5.11

⁹ www.patient.co.uk/health/Duchenne-Muscular-Dystrophy.htm Website accessed 27.5.11

¹⁰ Duchenne Muscular Dystrophy, Muscular Dystrophy Campaign, Factsheet http://www.muscular-dystrophy.org/about_muscular_dystrophy/conditions/97_duchenne_muscular_dystrophy Website accessed 27.5.11

¹¹ Personal e-mail correspondence with Kristina Elvidge, Muscular Dystrophy Campaign on 27.5.11.

Previously, data suggested that the chances of a person with DMD living to 25 years of age in the 1960s were 0%, whereas the chances of living until 25 years of age in the 1990s increased to 54%.¹² Although the figures on survival rates vary depending on the nature of the study and the treatments given, another more recent study (2009) with 43 DMD patients estimated that the probability of survival to age 30 years was 85%.¹³

5. How many people suffer from DMD?

DMD usually affects boys, but very rarely, the condition can affect girls too. Females with a mutant X chromosome will not have DMD, but they will be carriers of the disorder. Those very rare females who have DMD are believed to either carry mutant genes on both X chromosomes, or have an inactivated healthy X chromosome.¹⁴

Precise and up-to-date information on patient numbers have been sparse, as only a small number of epidemiological studies have been published. Accurate patient numbers are particularly important for the provision of services, for tracking the impact of the disease, and in terms of the logistics required for conducting clinical trials.

- Figures suggest that prevalence of DMD is around 1 in 2,400 male births¹⁵ and 1 in 50,000,000 female births.¹⁶
- About 100 boys with DMD are born in the United Kingdom each year. There are about 1500 known boys with the condition living in the UK at any one time.¹⁷
- In relation to Northern Ireland, the number of local cases of DMD is approximately 67 boys/young men (1,685,000 / 60,512,000 x 2400).
- Extrapolating these figures to the world prevalence (with a population of 6.92 billion) would be approximately 275,000 cases.¹⁸

[Please note, these figures are purely indicative].

6. Treatment Options

At present, there is no known cure for DMD, yet sufferers require specialist treatment from a variety of healthcare professionals. Research continues to search for a cure and more appropriate treatments.

Specialised medical care can make an enormous difference to length and quality of life.

¹² Care and management of Duchenne Muscular Dystrophy- a multidisciplinary approach: Online at http://admin.duchenne-community.com/public/uploads/pdf/20090312135021_Goemans%20-%20care%20and%20management%20of%20DMD%20Bangalore%20final%20for%20website.pdf

¹³ Kohler et al (2009) "Disability and survival in Duchenne muscular dystrophy" *J Neurol Neurosurg Psychiatry* 2009; **80**:320-325

¹⁴ Webb CL. Parents' perspectives on coping with Duchenne muscular dystrophy. *Child Care Health Dev.* 2005 Jul; **31**(4):385-96.

¹⁵ Other studies cite 1 in 3,500 male births, see www.cks.nhs.uk/patient_information_leaflet/muscular_dystrophy# Website accessed 31.5.11

¹⁶ <http://www.bupa.co.uk/individuals/health-information/directory/d/duchenne-muscular-dystrophy> Website accessed 27.5.11

¹⁷ Available online at www.muscular-dystrophy.org/about_muscular_dystrophy/conditions/97_duchenne_muscular_dystrophy

¹⁸ Personal e-mail correspondence with Kristina Elvidge, Muscular Dystrophy Campaign on 27.5.11.

Current treatment is aimed at managing the symptoms by using physiotherapy and physical aids such as leg splints, wheelchairs and so forth. Steroids (glucocorticoid corticosteroids) and growth hormones are also used to manage the symptoms but cannot protect muscles from decline.¹⁹ Available literature stresses the importance to keep children as mobile as possible for as long as possible. Regular exercises such as swimming and stretching have been found to be beneficial. In addition maintaining a healthy diet is important as children with DMD can be overweight due to steroid medication, or on the other hand underweight, due to either muscle mass loss or swallowing difficulties.

As the condition progresses, regular check-ups are required, for example heart and lung checks, and orthopaedic care for bones and joints. People with DMD may develop osteoporosis due to lack of mobility or as a result of steroid treatment. In some cases, surgery may be needed to repair postural deformities like scoliosis.²⁰

Yearly heart scans are necessary once DMD has been diagnosed. Associated heart complications may be treated with ACE inhibitors or beta blockers. Respiratory infections are treated with antibiotics and a ventilator may be required to aid breathing in the later years.²¹

6.1 Treatment services in Northern Ireland

Survey research carried out by the UK charity 'Action Duchenne' illustrated the need for improved care and specialist services for DMD sufferers in Northern Ireland. The survey revealed that parents felt that care was not adequate when compared to that in England, and that no local centres of excellence existed. Due to the lack of epidemiological data and the rarity of muscular dystrophy conditions, less specialist, multi-disciplinary treatment services are available. In addition, funding is often overlooked across the local landscape.²² Health professionals and parents alike have lobbied the government for more appropriate services for Northern Ireland, and a number of these issues are highlighted in the 2009 report by the Muscular Dystrophy Campaign entitled "*Improving Specialist Care, Support and Independence.*"²³

7. Is there any on-going research into the condition?

There is a variety of research taking place worldwide to improve treatment of DMD and to find a possible cure. Some of the current research is exploring:

¹⁹ <http://www.bupa.co.uk/individuals/health-information/directory/d/duchenne-muscular-dystrophy#textBlock199337>

Website accessed 31.5.11

²⁰ NHS choices website www.nhs.uk/Conditions/Muscular-dystrophy/Pages/Treatment.aspx

²¹ <http://www.bupa.co.uk/individuals/health-information/directory/d/duchenne-muscular-dystrophy#textBlock199337>

Website accessed 27.5.11

²² Muscular Dystrophy Campaign (2010) "Muscle Disease: the impact. Incidence and prevalence of neuromuscular conditions in the UK"

²³ Muscular Dystrophy Campaign February 2009 "Improving Specialist Care, Support and Independence" http://www.muscular-dystrophy.org/assets/0000/5349/Build_on_Found_NI_report.pdf Website accessed 27.5.11

- What is the best type and dose of steroid treatment to help maintain muscle strength?
- Can gene therapy be used to cure DMD or prevent loss of muscle? This involves a type of gene therapy called 'exon skipping' and initial trial results are promising.
- Stem cell therapy - using cells that produce normal dystrophin.
- A form of pharmacological (drug) treatment may be feasible, helping to produce a protein called 'utrophin' which is similar to the missing dystrophin.

The most promising research into DMD is “exon skipping” (gene therapy). Exon skipping works by masking the faulty part of the dystrophin gene, allowing a shortened but functional dystrophin protein to be produced. Gene therapy for DMD aims to increase the amount of dystrophin protein by delivering a dystrophin gene to the muscle. Viruses, which have been modified to prevent them causing illness, can act as efficient carriers for delivering micro-dystrophin into muscle cells.²⁴

Scientists have shown this technique to be effective in a mouse model of DMD (the mdx mouse) and in human DMD muscle cells grown in the laboratory. A phase 1 clinical trial involving nine boys with DMD was completed in December 2008 whereby a 'molecular patch' (called AVI-4658) was injected into a muscle in the foot. This resulted in dystrophin production in this muscle and no serious side-effects were observed.²⁵ Preliminary results from the phase 2 of the trial were released in June 2010. In this trial the molecular patch was injected into the blood stream of boys with DMD. At the higher doses, dystrophin production was seen in muscle biopsies taken at the end of the trial.

Three companies involved in various clinical trials of this therapy include Prosensa, GSK and AVI Biopharma. Further details of the 3rd phase of the trial are provided in Appendix 1.

Academic research

Academic studies are also looking to refine the exon skipping technique. For example:

- Researchers at the University of Oxford are completing a two year study (commencing in 2009) entitled “*Optimization of “molecular patches” to restore dystrophin production in boys with Duchenne muscular dystrophy*”²⁶
- Another study at Oxford is underway to increase the amount of ‘utrophin’ protein, in essence to compensate for the missing dystrophin.²⁷ Entitled “*Upregulation of utrophin for DMD therapy*”, the study has been successful in

²⁴ Muscular Dystrophy Campaign www.muscular-dystrophy.org/about_muscular_dystrophy/research_faqs/612_what_is_exon_skipping_and_how_does_it_work Website accessed 31.5.11

²⁵ Muscular Dystrophy Campaign www.muscular-dystrophy.org/about_muscular_dystrophy/research_faqs/612_what_is_exon_skipping_and_how_does_it_work Website accessed 27.5.11

²⁶ Muscular Dystrophy Campaign www.muscular-dystrophy.org/research/grants/current_grants/1593_patrick_research_fellowship_optimization_of_molecular_patches_to_restore_dystrophin_production_in_boys_with_duchenne_muscular_dystrophy

²⁷ Muscular Dystrophy Campaign http://www.muscular-dystrophy.org/research/news/3743_utrophin_drug_shows_promise_for_duchenne_and_becker_muscular_dystrophies Website accessed 27.5.11

reducing muscle weakness in mice²⁸ and media reports suggest it will offer hope for the future for those suffering from DMD.²⁹

- Another study at the University of London is seeking to introduce a healthy copy of the faulty dystrophin gene using a virus. This study is entitled *“Enhancing the Therapeutic Functionality of Adeno-associated Virus (AAV) Vectors Encoding Dystrophin for Duchenne Muscular Dystrophy Gene Therapy”*.³⁰

A variety of other trials are happening in different countries. For example, in the US a clinical trial for a heart drug (Revatio) to improve heart function of DMD patients is being examined.³¹ Other examples include the use of monitoring DMD using Magnetic Resonance Imaging (MRI) to determine whether non-invasive MRI outcome measures can replace muscle biopsies in evaluating the effectiveness of new treatments in future clinical trials.³²

The Action Duchenne website also provides a list of funded DMD research partnerships and achievements over the last number of years.³³ The charity has worked with Duchenne Trusts across the world including Charley's Fund, Gavriel Meir Trust, Duchenne Ireland, ICE and the Matthew and James Trust in Ireland to fund new research.

Clinical trials are also progressing with Ataluren (an oral drug) designed to enable the formation of a functioning protein. The study seeks to ascertain if certain doses of the drug can demonstrate clinical benefit; however results of the 2b trial phase (2010) for those with DMD have proved inconclusive and further analysis will be required.³⁴

It is evident that clinic research studies have made considerable strides in understanding the nature of DMD a various approaches have been taken. However further work and additional funding will be required before a long term treatment solution or possible cure is found.

²⁸ Muscular Dystrophy Campaign www.muscular-dystrophy.org/research/grants/current_grants/513_utrophin_up-regulation_a_potential_treatment_for_duchenne_muscular_dystrophy Website accessed 31.5.11

²⁹ BBC news online www.bbc.co.uk/news/health-13279779 Website accessed 27.5.11

³⁰ Muscular Dystrophy Campaign www.muscular-dystrophy.org/research/grants/current_grants/1591_investigating_ways_to_improve_the_efficiency_of_gene_therapy_for_duchenne_muscular_dystrophy Website accessed 27.5.11

³¹ DuchenneConnect www.duchenneconnect.org/index.php?option=com_content&view=article&id=245%3Arevatio-for-heart-disease-in-duchenne-muscular-dystrophy-a-becker-muscular-dystrophy-reverse-dbmd&catid=54%3Aclinical-trials-news&Itemid=313&lang=es

³² DuchenneConnect https://www.duchenneconnect.org/index.php?option=com_content&view=article&id=246%3Anow-recruiting-mri-and-biomarkers-for-duchenne-muscular-dystrophy-study-imagingdmd&catid=54%3Aclinical-trials-news&Itemid=313&lang=es Website accessed 27.5.11

³³ Action Duchenne www.actionduchenne.org/r-nav/438.jsp Website accessed 27.5.11

³⁴ www.muscular-dystrophy.org/assets/0001/6230/2010-04-16_Final_Summary_of_Ataluren_Data_at_AAN.pdf Website accessed 27.5.11

Appendix 1

Phase 3 study of the effect of a drug to skip exon 51 (GSK2402968) on the muscle function of boys with Duchenne muscular dystrophy

- **Funder:** GlaxoSmithKline **Start Date:** December 2010
- **Expected End Date:** December 2012
- **Status:** Recruiting
- **Location of trial:** Asia, Europe, North America, Other

What is the aim of the trial?

This phase 3 trial will test a drug (GSK2402968) that has been designed to skip exon 51 of the dystrophin gene. The investigators will be assessing the effect of GSK2402968 on the muscle function of boys with Duchenne muscular dystrophy and will continue to monitor the safety of the drug.

A phase 1/2 trial of GSK2402968 (previously known as PRO051) has already been completed and production of a shortened version of dystrophin protein was observed in muscle biopsies with no serious side effects. Previous trials however have not had enough participants treated for a sufficiently long time to determine if this production of dystrophin leads to an improvement in muscle function. This trial will primarily assess muscle function using the six minute walk test.

GSK have in-licensed GSK2402968 from Prosensa who led early clinical development. This means that GSK have a license to develop and market it. Exon skipping of exon 51 is also being trialled by the company AVI Biopharma using a chemical formulation of molecular patch that differs slightly from that used by Prosensa.

Who can be involved in the trial?

This trial aims to recruit 180 boys with Duchenne muscular dystrophy aged 5 years or older who are still able to walk at least 75 metres in six minutes. They must also have one of the mutations in the dystrophin gene that is correctable by GSK2402968. They must have been taking corticosteroids for at least 6 months and be on a stable dose. Some heart, liver and kidney problems, the use of certain medications and participation in some other clinical trials may make patients ineligible from the study.

What happens during the trial?

Participants will be randomly assigned to either the treatment group or the placebo group. A placebo is an inactive substance designed to resemble the drug being tested. It is used to rule out any benefits a drug might exhibit because the recipients believe they are taking it. Neither the participants nor the clinicians will know who is receiving the placebo.

Both groups will receive a once weekly injection under the skin for 48 weeks. The main way to assess how the drug is affecting muscle function will be to measure the distance the participants can walk in six minutes. Other measures of muscle strength and breathing tests will also be done. Muscle biopsies to look for dystrophin protein will take place and periodically throughout the trial blood samples will be taken and general physical checks will be done. Changes in quality of life will be assessed by the completion of questionnaires.

Where is the study taking place?

The study will be taking place in up to 18 countries. The countries that have been announced so far are: • France • Germany • Japan • South Korea. It is expected that

sites in Canada and South America will also be announced in the near future and more countries will be added over time.

How could the results of the trial benefit patients?

The results from this trial will start to answer questions about whether GSK2402968 has a positive effect on the muscles of people with Duchenne who have mutations in the region of exon 51 of the dystrophin gene. If this trial is successful in proving that this treatment is effective and safe, GSK will then be in a position to apply to regulatory bodies for permission to market it and make it more widely available.

Trial study number:

NCT01254019