Background to the EMBARK study and the medication Delandistrogene Moxeparvovec

Disclosure
This document contains general information about the Duchenne Muscular Dystrophy EMBARK study and is not intended as specific medical advice.

Delandistrogene Moxeparvovec is an investigational medicine (only approved in the US, UAE and Qatar) that is being studied for the treatment of boys with Duchenne Muscular Dystrophy. Delandistrogene Moxeparvovec has not been approved by the European Medicines Authority (EMA) or the Medicines & Healthcare products Regulatory Agency (MHRA).

The efficacy and safety of Delandistrogene Moxeparvovec are currently being studied.

Patients should talk with their healthcare provider for information and advice about their condition, including any current or potential treatments.

1. What is delandistrogene moxeparvovec?

Delandistrogene moxeparvovec is a gene therapy that encodes for the micro-dystrophin protein. Micro-dystrophin is an abbreviated, or shorter length version of the dystrophin protein.[1,5]

Gene therapies are made up of a vector, a promoter and a transgene.[1,5]

a. Vector: a vehicle used to carry the gene of interest into the target cells. These vectors may be derived from a virus (viral vectors) such as adeno-associated virus (AAV).
b. Promoter: a genetic "switch" that works to promote expression of the transgene in specific tissues.
c. Transgene: this is the gene that is being transferred. In this care it would be the engineered version of the micro-dystrophin gene, designed to produce an engineered, functional form of the micro-dystrophin protein.

Delandistrogene moxeparvovec combines a specific vector, promoter and transgene that are intended to maximise delivery of the transgene that encodes for the micro-dystrophin protein.[1]

Delandistrogene moxeparvovec component[3,4,6]	**Function**
AAVrh74 vector	An adeno-virus associated vector derived from rhesus monkeys with a potential low capability of stimulating an immune response. This vector carries the transgene.
MHCK7 promoter	The 'switch' that turns on the micro-dystrophin transgene in target muscle cells. The MHCK7 promoter is associated with high levels of expression in skeletal muscles including the diaphragm, and the heart muscle.

Micro-dystrophin transgene	Produces the micro-dystrophin protein, an engineered protein that retains key functional domains of the full-length dystrophin protein.

2. What is the EMBARK study?

EMBARK is the first global phase 3 study of a gene therapy in Duchenne Muscular Dystrophy. It aims to evaluate the efficacy and safety of delandistrogene moxeparvovec in boys who have Duchenne Muscular Dystrophy, are able to walk unassisted and are aged from 4 to 7 years old (inclusive).

The study is two years long during which each child receives one infusion (in the vein) of delandistrogene moxeparvovec and one infusion (in the vein) of placebo (which has no treatment effect), one year apart. Half the boys were given delandistrogene moxeparvovec in year one, followed by placebo in year two. While the other half were given placebo in year one followed by delandistrogene in year two. The selection of the boys in each of the groups was done randomly.

The entire study is double blind which means that none of the boys, their caregivers, healthcare professionals or the trial site knows which child received delandistrogene moxeparvovec in year one followed by placebo in year two, and which child received placebo in year one followed by delandistrogene in year two.[1] All boys are monitored for one year after receiving each of their delandistrogene moxeparvovec / placebo infusions.

3. What is the design of the EMBARK study?

Whether or not a patient is eligible for a study is based on the inclusion and exclusion criteria of that study. We have listed the key inclusion and exclusion criteria for the EMBARK study below. Other inclusion or exclusion criteria could apply.[7]

<u>Key inclusion criteria for EMBARK include*:</u>[1]

1. Boys who are able to walk unassisted and who are 4 years of age through to 7 years of age at the point of randomisation of the study i.e. the point when boys are randomly assigned to either the group receiving delandistrogene moxeparvovec in year one followed by placebo in year two, or to the group receiving placebo in year one followed by delandistrogene moxeparvovec in year two.
2. Definitive diagnosis of DMD based on documented clinical findings and prior genetic testing.
3. Confirmed DMD mutation fully contained between exons 18 to 79 (inclusive) that is expected to lead to the absence of dystrophin protein:
    a. Participants with mutations between or including exons 1–17 or mutations fully contained within exon 45 (inclusive) are not eligible
    b. Other mutations of uncertain significance are not eligible.
4. NSAA score at time of screening must be >16 and <29.
5. Time to Rise at time of screening must be <5 seconds
6. Ability to cooperate with motor assessment testing.
7. Stable daily dose of oral corticosteroids for at least 12 weeks prior to screening, and the dose is expected to remain constant throughout the study (except for modifications to accommodate weight changes).

8. rAAVrh74 antibody titers are not elevated** (the study protocol defines the limits). This is necessary because the body may produce antibodies to rAAVrh74.

Key exclusion criteria for EMBARK include:*[1]

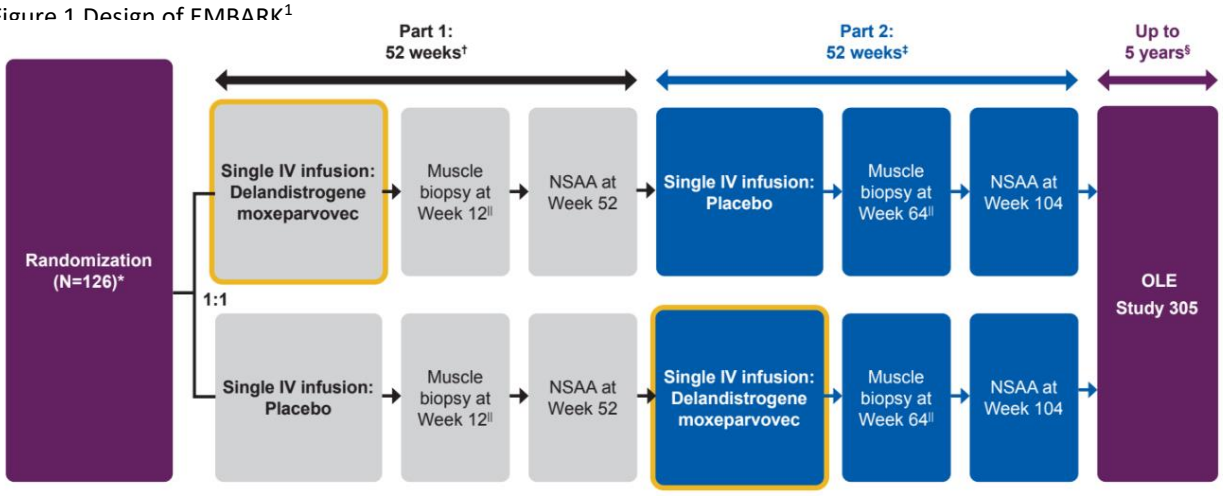
1. Previous exposure to gene therapy, investigational medication, or any treatment designed to increase dystrophin expression (the study protocol defines the time range for the previous exposure).
2. Abnormalities in diagnostic evaluations and laboratory tests as specified in the study protocol.
3. Presence of any other clinically significant illness, medical condition, or requirement for chronic drug treatment that, in the opinion of the investigator, creates unnecessary risk for gene transfer.

* other inclusion or exclusion criteria could apply[7]
** low levels of antibodies to the vector are required as high levels may cause an immune response[5]

Trial design and treatment groups:

- The trial consists of two parts. During part 1 which lasted for a year, half of the boys were randomised to receive a single infusion (in the vein) of delandistrogene moxeparvovec and the other group received a single infusion (in the vein) of placebo. Randomisation took into account the age of the child (either 4 to 5 years or 6 to 7 years) and their NSAA score when entering the study (either ≤22 points or >22 points).
- Part 2 will start at the end of the first year and will also last for a year. During part 2 those boys who had received delandistrogene moxeparvovec in the first year will receive a single infusion (in the vein) of placebo, while those who had received placebo in the first year will now receive a single infusion (in the vein) of delandistrogene moxeparvovec.
- All trial participants will therefore receive a single infusion of delandistrogene moxeparvovec and a single infusion of placebo.
- All participants will have a muscle biopsy done 12 weeks after each of their infusions.
- The entire study is double blind which means that none of the patients, their caregivers, healthcare professionals or the trial site will know whether a child is receiving delandistrogene moxeparvovec or placebo until the unblinding of the study. (Figure 1).[1]
- The EMBARK study duration is approximately 108 weeks (2 years), with a pre-infusion period of 31 days and a treatment and follow-up period of 104 weeks.[1]
- After the end of Part 2, all participants will be given the opportunity to enroll into the long-term extension study.[2]

Figure 1 Design of EMBARK[1]



**N=120 was the target recruitment. †Double-blind, placebo-controlled. ‡Patients, caregivers, investigators, and site staff remain blinded. §Separate, planned open-label study (EXPEDITION; Study 305) of up to 5 years post-delandistrogene moxeparvovec infusion. ||Only a subset of patients will receive a muscle biopsy for expression assessments.*

Outcome measures:

- The assessment is the change in NSAA total score from the start of the study (baseline) to Week 52 (Part 1)†.[1]

- Secondary endpoints include:[1]
  - Quantity of delandistrogene moxeparvovec micro-dystrophin expression at Week 12 as measured by the muscle biopsy (Part 1)
  - Change from start of the study (baseline) to Week 52 in Timed Function Tests: Time To Rise, 100 meter walk/run, time to ascend 4 steps, and 10 meter walk/run (Part 1)
  - Change in Stride Velocity 95th Centile (this is an electronic measurement of movement capturing peak performance and speed) from start of the study (baseline) to Week 52 as measured by a wearable device (Part 1)
  - Change in Patient Reported Outcome Measurement Information System score per domain (mobility and upper extremity function) from start of the study (baseline) to Week 52 (Part 1)
  - Number of skills gained or improved at Week 52 as measured by the North Star Ambulatory Assessment (Part 1)
  - Incidence of treatment-emergent Adverse Events, Serious Adverse Events, and Adverse Events of special interest; clinical changes in vital signs, physical examination findings, safety laboratory assessments, Electrocardiograms and Echocardiograms

† Please note that at this stage (the end of part 1), only half would have received delandistrogene, while half would have received placebo. Remember that during Part 2, those who would have had placebo in part 1 will be given delandistrogene moxeparvovec in part 2 and vice versa

4. How is delandistrogene moxeparvovec intended to treat Duchenne Muscular Dystrophy?

1. In the clinical trials Delandistrogene Moxeparvovec is administered as a one time treatment in one dose by a single infusion into the vein.[1]

2. Delandistrogene moxeparvovec encodes for micro-dystrophin which is a shortened version of the dystrophin protein found in normal muscle cells. The EMBARK study aims to show whether the treatment with this micro-dystrophin leads to meaningful differences in motor function as assessed by the NSAA.[5]
3. Roche continues to monitor people who have received delandistrogene moxeparvovec. Roche aims to collect longer-term data to assess the ongoing efficacy and safety profile of delandistrogene moxeparvovec.

5. What are the licensing arrangements for delandistrogene moxeparvovec in the UK?

Roche and Sarepta have entered into a licensing agreement in relation to the development and commercialisation of delandistrogene moxeparvovec. Sarepta is responsible for the Clinical Development Program and the commercialisation of delandistrogene in the US. Roche is responsible for the commercialisation outside of the US - including the UK.

All medicines in the UK require a licence from the Medicines and Healthcare products Regulatory Authority (MHRA). Roche is working with the MHRA to understand the potential licensing routes for this therapy in the UK. It is important to note that the potential licensing of delandistrogene moxeparvovec is subject to the outcome of the EMBARK study.

Licensing is just the first step. Roche UK are also working with NICE (The National Institute for Health and Care Excellence), SMC (Scottish Medicines Consortium), NHS (National Health Service) in England and Scotland and other stakeholders including those in Northern Ireland & Wales, so that potential new treatments such as delandistrogene moxeparvovec (if the outcome of the trial is positive) can be made available to patients/families via our National Health Service as quickly as possible.

It is important to consider that change is needed in the way relevant public bodies such as NICE & SMC assess the potential value of new treatments and how medicines are funded through the NHS so patients in the NHS have the best possible chance of being treated with innovative new treatments .

References:

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