23 June 2023

Dear members of the European Alliance of Neuromuscular Disorders Association,

Following your request for regular updates, it is a great pleasure to share the news that the US Food and Drug Administration (FDA) has approved delandistrogene moxeparvovec-rokl (also known as SRP-9001) for the treatment of ambulatory children (those who are able to walk unassisted) aged 4 through 5 years with Duchenne muscular dystrophy (DMD) and a confirmed mutation in the *DMD* gene.[1] Delandistrogene moxeparvovec-rokl is contraindicated in patients with any deletion in exons 8 and/or 9 in the *DMD* gene. In the US, delandistrogene moxeparvovec-rokl will be marketed as Elevidys™ (Ah-LEV- ah-dis) and is the first gene therapy approved for Duchenne.

Duchenne is characterised by mutations in the dystrophin gene that result in the lack of dystrophin protein. In the absence of dystrophin, which is required to strengthen and protect muscles, muscles become weakened and damaged.[2] Delandistrogene moxeparvovec addresses the root genetic cause of the disease by delivering a gene that codes for a functional shortened form of the dystrophin protein to muscle cells known as Elevidys micro-dystrophin. Delandistrogene moxeparvovec is given as a one-time intravenous (IV) infusion. Roche is developing delandistrogene moxeparvovec in partnership with Sarepta Therapeutics and is responsible for bringing this treatment to patients across the rest of the world (excluding the US).

The Biologics License Application (BLA) submitted to the FDA included safety and efficacy data from three Phase 1 and Phase 2 studies for delandistrogene moxeparvovec:[3] Study 101 (NCT03375164), Study 102 (NCT03769116), Study 103 (also known as ENDEAVOR, NCT04626674) and an integrated analysis across these three clinical studies comparing functional results to a propensity-score-weighted external control*.[4,5,6] Delandistrogene moxeparvovec-rokl was approved under the FDA's Accelerated Approval pathway**.

To qualify for this approval pathway, a confirmatory trial to verify the results of the studies submitted for a BLA must be completed. The fully enrolled, global Phase 3 EMBARK study (NCT05096221) will serve as the confirmatory study for delandistrogene moxeparvovec-rokl. This means that, if the trial meets its objectives, the FDA will assess conversion to traditional approval and the results will inform its decisions moving forward regarding the potential for a broader indication. Sarepta will work as quickly as possible to share data from EMBARK with the FDA. The top-line results are expected at the end of this year.[8]

Following this announcement, we deeply appreciate that many families, caregivers and people living with Duchenne will be seeking to understand if and when this medicine is likely to receive approval in their country.

We know that time is muscle, and time has incredible value for every family touched by Duchenne. At Roche, our unwavering focus remains on working with urgency to file regulatory applications with health authorities around the world to ensure delandistrogene moxeparvovec reaches eligible children as quickly as possible. An overview of our regulatory application plans is below, based on the latest information we have available. (Please do note that the status of our applications may change, depending on the requirements of health authorities.)

- In countries that can accept applications based on Phase 1 and Phase 2 data for delandistrogene moxeparvovec, we are already engaging with health authorities and plan to submit applications as soon as possible. These countries include Bahrain, Brazil, Israel, Kuwait, Oman, Qatar, Saudi Arabia, Singapore and the United Arab Emirates.

- The European Medicines Agency (EMA) have indicated that the inclusion of clinical trial data from the Phase 3 EMBARK study for delandistrogene moxeparvovec are vital for their assessment. If the EMBARK data are supportive, we expect to submit marketing authorisation applications to the EMA and to other health authorities as soon as possible.

The FDA approval is the first of what we hope will be many more encouraging updates to the Duchenne community as delandistrogene moxeparvovec continues its journey to reach those who need it. Our sincere gratitude and appreciation goes out to the families who are participating in Duchenne research and the tireless efforts of patient groups, clinical trial sites and staff - achievements like these that benefit the entire community would not be possible without you. We are humbled to be part of this resilient community.

We expect that you may receive questions from your community about today's news, so we have included some additional information below for you and your members. If you have any other questions about this update, please do not hesitate to contact me. We look forward to providing further updates as they become available.

Sincerely,

Fani Petridis, on behalf of the Roche Global DMD Team

<u>Questions and answers</u>

1. **How do Roche and Sarepta work together?**
    - Roche and Sarepta work together in a partnership and joint development programme.[9]
        - Sarepta is responsible for conducting clinical studies as well as managing regulatory approval and the commercialisation of delandistrogene moxeparvovec-rokl in the US.
        - Roche is responsible for regulatory approval, Health Technology Assessment appraisal and bringing delandistrogene moxeparvovec to patients across the rest of the world.
        - Sarepta is responsible for the manufacturing of delandistrogene moxeparvovec and will supply the product to Roche for distribution.

2. **What does the FDA approval mean?**

- The FDA has approved delandistrogene moxeparvovec-rokl, in the US, for the treatment of ambulatory children (those who are able to walk unassisted) aged 4 through 5 years with Duchenne muscular dystrophy and a confirmed mutation in the *DMD* gene.[1]
- If the Phase 3 EMBARK trial meets its objectives, the FDA will assess conversion to traditional approval and the results will inform the Agency's decisions moving forward regarding the potential of a broader label.[7] The top-line results are expected at the end of this year.[8]

3. What is the safety profile of delandistrogene moxeparvovec?

- To date, the safety profile of delandistrogene moxeparvovec is consistent across three Phase 1 and 2 clinical trials: Study 101 (NCT03375164), Study 102 (NCT03769116) and Study 103 (also known as ENDEAVOR, NCT04626674). Across these three clinical trials:[10]
  - There were no deaths.
  - No adverse events (AEs) led to study discontinuation.
  - Less than 10% of patients experienced treatment-related SAEs. The SAEs were:
    - Vomiting; increased liver enzymes (transaminases); rhabdomyolysis; liver injury; immune-mediated myositis; myocarditis.
  - The most frequently observed treatment-emergent AE was vomiting, nausea, decreased appetite and upper respiratory tract infection.
  - No clinically relevant complement activation was observed.
  - There have been no signs of liver failure reported across the delandistrogene moxeparvovec clinical studies.

4. When are you planning to apply for regulatory approval in Europe and the rest of the world?

- If the results of the ongoing Phase 3 EMBARK study (Study 301, NCT05096221) are supportive, we expect to submit marketing authorisation applications to the EMA and to health authorities in other countries as soon as possible.
- With the US FDA approval granted, we are already engaging with health authorities in countries that can accept applications based on Phase 1 and Phase 2 data for delandistrogene moxeparvovec. We plan to submit applications in Bahrain, Brazil, Israel, Kuwait, Oman, Qatar, Saudi Arabia, Singapore and the United Arab Emirates as soon as possible.

5. Why did the FDA approve the use of delandistrogene moxeparvovec-rokl to ambulatory patients aged 4–5 years?

- Results from Study 102, a double-blind placebo-controlled Phase 2 study, were a significant part of the data package that was submitted to the FDA by Sarepta.
- In this study, a clinical advantage was seen in the 4–5 year-old age group treated with delandistrogene moxeparvovec compared to placebo. The FDA may consider an expansion of the delandistrogene moxeparvovec-rokl label based upon the review of the Phase 3 EMBARK data.[7]

6. Why has the FDA restricted the use of delandistrogene moxeparvovec-rokl in patients with any deletion in exons 8 and/or 9 in the DMD gene?

- In clinical trials, immune-mediated myositis has been observed approximately one month following delandistrogene moxeparvovec infusion in patients with deletion mutations involving exons 8 and/or 9 in the DMD gene. Symptoms of severe muscle weakness including dysphagia, dyspnea and hypophonia were observed.
- Limited data are available for delandistrogene moxeparvovec treatment in patients with mutations in the DMD gene between exons 1 to 17 and exons 59 to 71. Patients with deletions in these regions may be at risk for a severe immune-mediated myositis reaction.

7. **Do you expect delandistrogene moxeparvovec to be approved for the same indication / label outside the US?**
   - Different health authorities act independently, following distinct processes with different filing requirements. Although their ultimate goals are the same for their geographical regions, they have distinct regulations and procedures, meaning there are differences in how medicines are approved.
   - Whether these health authorities will impose the same or a more restrictive label is yet to be determined. Roche is actively engaging with health authorities to discuss the registration pathway for delandistrogene moxeparvovec. Final labelling will depend on the health authorities' decisions for each country.

8. **In countries where delandistrogene moxeparvovec is not yet approved / awaiting approval, will it be possible for patients outside of the US to access it?**
   - Roche recognises that there is a significant unmet medical need for those living with Duchenne. As a high priority, we are actively working with reimbursement authorities to evaluate the most appropriate pathways to bring delandistrogene moxeparvovec to people living with Duchenne as quickly as possible and in a sustainable way.
   - We are aware that in a selected number of countries physicians will be able to request access for delandistrogene moxeparvovec on a paid-for, named-case basis (often referred as Named Patient Supply), in line with local regulations and based on applicable company policy. We are working towards being able to respond to such requests as received.

9. **How many patients have been treated with delandistrogene moxeparvovec so far?**
   - More than 150 people have been treated with delandistrogene moxeparvovec in clinical trials to date.

10. **Which delandistrogene moxeparvovec clinical trials are currently open for recruitment?**
    - ENVISION (also known as Study 303, NCT05881408) is a global Phase 3 clinical study that aims to evaluate the safety and efficacy of delandistrogene moxeparvovec, in non-ambulatory (those who are not able to walk unassisted) and older ambulatory (those who are able to walk unassisted) boys. Roche will be sharing further information on the study timelines and locations outside of the US after the summer.

11. **When can we expect to hear the price of delandistrogene moxeparvovec? Will it be the same in all countries?**
    - Roche is responsible for bringing delandistrogene moxeparvovec to patients outside of the US. Roche is not involved in setting the US price.

- We are committed to appropriately pricing delandistrogene moxeparvovec in a sustainable way, reflecting the value it brings to patients, their families and health systems and society.
- Although we are already engaging with reimbursement bodies in countries where we intend to submit marketing authorisation applications, it is too soon for us to advise on the price.

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**Propensity-score-weighted external control is a statistical method used to estimate the effectiveness of a medical treatment or intervention when a large enough placebo controlled group is not feasible, using real-world data as an external control.*

***The FDA Accelerated Approval programme allows treatments for serious conditions that fill an unmet medical need to be approved based on a surrogate endpoint, or biomarker data that are likely to be predictive of clinical benefit. Pharmaceutical companies are still required to conduct studies to confirm the anticipated clinical benefit. If the confirmatory trial shows that the treatment actually provides a clinical benefit, then the FDA grants traditional approval.*

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