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Long-term effect of ataluren in patients with a specific type of genetic mutation leading to Duchenne muscular dystrophy

The full title of this article:

Ataluren delays loss of ambulation and respiratory decline in nonsense mutation Duchenne muscular dystrophy patients

How to pronounce:

- **Ataluren:** <a-ta-LEWR-ren>
- **CINRG:** <SIN-ər-jee>
- **Duchenne muscular dystrophy:** <doo-SHEN MUH-skyoo-lər DIH-strə-fee>
- **Dystrophin:** <DIH-strə-fin>

Why was this analysis done?

Duchenne muscular dystrophy (DMD) is a rare genetic disease that affects the muscles and mostly occurs in boys.

It is progressive, which means it gets steadily worse over time. DMD is caused by changes in the DNA of the *DMD* gene. These changes are called mutations. The *DMD* gene contains the code for the cell to make a protein called dystrophin. Dystrophin has an important role in protecting the muscle from progressive damage. Mutations in the *DMD* gene lead to less or no dystrophin being made, which results in muscle weakness. Over time, DMD causes increasing weakness in the leg, arm, lung and heart muscles. People with DMD have a short life expectancy, often living to 20–40 years old, even with current treatments available. Researchers and doctors are looking for better ways to treat DMD. There are treatments available, and ongoing research is teaching us more about them, especially regarding their long-term effects over several years.

This analysis included participants with a certain type of DMD, called **nonsense mutation DMD (nmDMD)**. A nonsense mutation is a change in the DNA that causes the protein production to stop before it is completed. The resulting protein does not work properly. About 10–15% of patients with DMD have a nonsense mutation in the *DMD* gene and are therefore referred to as having nmDMD.

Standard of Care (SoC) is the usual healthcare provided to patients with DMD according to the recommended guidelines. SoC for DMD includes the use of corticosteroids to treat the symptoms of muscle weakness.

Ataluren* is a drug that is taken by mouth three times every day. It is designed to work by allowing the production of a complete functional dystrophin protein when a nonsense mutation is present in the *DMD* gene. This helps to protect muscle mass and extend muscle function specifically in patients with nmDMD.

Loss of walking ability and **worsening of lung function** are significant events in the progression of DMD and have a great effect on the lives of the patient and caregiver. Here, we measured the benefit of ataluren by assessing whether the drug could delay the onset of these events.

Study 019 was a multinational clinical trial that included participants who had been treated with ataluren in previous trials and therefore had been taking ataluren for a long time. In Study 019, ataluren was given to participants in addition to SoC. Overall, 94 male patients with nmDMD participated in the study for up to 4.5 years, which took place at 21 clinical sites in 10 different countries.

The Cooperative International Neuromuscular Research Group Duchenne Natural History Study **(CINRG DNHS)** collected health information on patients with DMD aged 2–28 years across nine countries between 2006 and 2016 to help understand the natural course of the disease.

*Ataluren is indicated for the treatment of DMD resulting from a nonsense mutation in the *DMD* gene in ambulatory patients aged 2 years and older in the European Member States and Iceland, Liechtenstein, Norway, Great Britain, Northern Ireland, Kazakhstan, Belarus, Israel, Brazil, the Republic of Korea and Russia, and those aged 5 years and older in Chile and Ukraine (under special state registration in Ukraine). In Brazil, the indication is restricted to pediatric male patients. The presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing (Ataluren Summary of Product Characteristics for respective countries; Ataluren Instructions for Use – Russia).

What was the aim of this analysis?

The aim of this analysis was to find out more about the effect of ataluren in participants with nmDMD for the duration of the study, especially relating to the age at loss of walking ability and the age at decline in lung function beyond a certain critical level.

The present analysis aimed to determine the effect of ataluren by comparing participants with nmDMD from Study 019 with patients with DMD from the CINRG DNHS. In the CINRG DNHS, participants were given SoC, including corticosteroids, but were not given ataluren. For this analysis, participants from the two studies were matched to one another based on common predictors of disease progression, such as the age at which they first experienced symptoms.

To determine the effectiveness of the drug, doctors measured the **participants' walking ability**. If a participant took longer than 30 seconds to run or walk 10 meters, this was recorded as loss of walking ability. Similarly, **lung function** was studied by measuring the maximum volume of air that the participants could forcibly exhale from their lungs, which is called the forced vital capacity (FVC). Patients with DMD whose FVC has decreased to below 60% of their predicted lung function are usually at the later stages of the disease. Patients at this point require mechanical support with breathing to help preserve their lung function.

What were the findings from this analysis?

Age at loss of walking ability

Participants who were treated with ataluren and SoC lost their walking ability later in life than participants who were treated with SoC only.

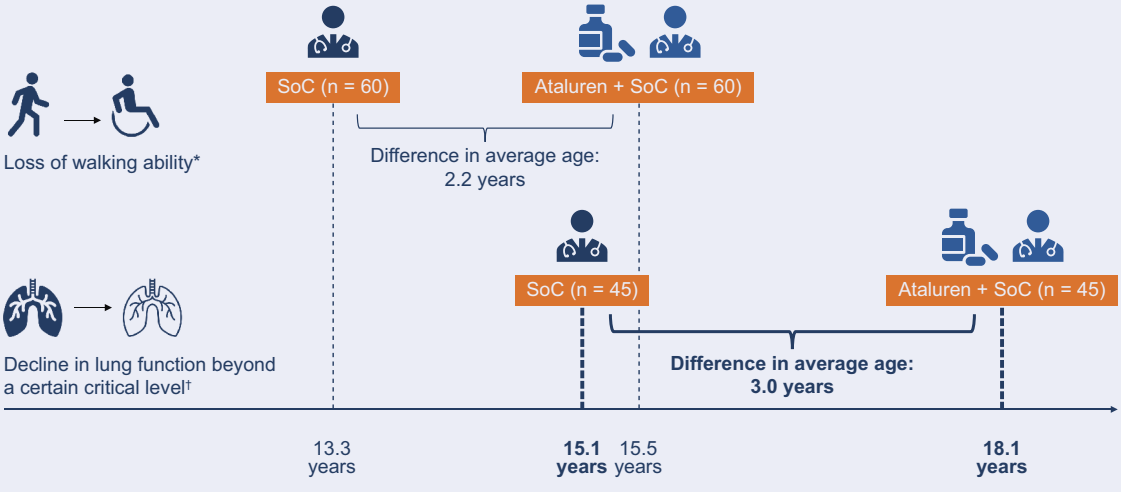
- The average age at which participants lost their ability to walk was **15.5 years** for participants with nmDMD from Study 019 (treated with ataluren and SoC) and **13.3 years** for participants with DMD from the CINRG DNHS (treated with SoC only).
- These results were calculated based on the data from 60 matched participants from each study.

Age at decline in lung function beyond a certain critical level

The lung function of participants who were treated with ataluren and SoC got worse later in life than that of participants who were treated with SoC only.

- The average age at which patients' lung function declined to an FVC of less than 60% of their predicted lung function was **18.1 years** for patients with nmDMD from Study 019 (treated with ataluren and SoC) and **15.1 years** for patients with DMD from the CINRG DNHS (treated with SoC only).
- These results were calculated based on the data from 45 matched participants from each study.

Ataluren treatment delayed the average age at which participants lost their walking ability and experienced a decline in their lung function beyond a certain critical level



*A patient was considered to have lost their walking ability if they took longer than 30 seconds to run or walk 10 meters.
†Decline in lung function was defined as the participant's FVC decreasing to below 60% of their predicted lung function.

What were the main conclusions from this analysis?

In this analysis, ataluren treatment in addition to SoC was shown to delay the age at which participants with nmDMD lost their walking ability and experienced a decline in lung function beyond a certain critical level compared with SoC alone in participants with DMD.

The findings from this analysis support previous results showing that ataluren treatment in combination with SoC can delay important signs of disease progression in patients with nmDMD.

Who sponsored this analysis?

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Useful additional reading

McDonald CM, Campbell C, Torricelli RE *et al*. Ataluren in patients with nonsense mutation Duchenne muscular dystrophy (ACT DMD): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 390(10101), 1489–1498 (2017).

A clinical trial that explored the safety and effectiveness of ataluren. Patients were given either placebo or ataluren. The effectiveness of the drug was tested by comparing the distance that participants could walk in 6 minutes.

Mercuri E, Muntoni F, Nascimento Osorio A *et al*. Safety and effectiveness of ataluren: comparison of results from the STRIDE Registry and CINRG DMD Natural History Study. *J. Comp. Eff.* 9(5), 341–360 (2020).

A study looking at the safety and effectiveness of ataluren in a real-world setting, using information from a patient registry (a system that uses observational methods to collect real-world data from patients).

Further information

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For more information on ataluren, please visit: https://www.ema.europa.eu/en/documents/product-information/translarna-epar-product-information_en.pdf