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Special report

European Medicines Agency review of ataluren for the treatment of ambulant patients aged 5 years and older with Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene

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1. Introduction

Duchenne muscular dystrophy (DMD) is a rare disease, with an overall estimated prevalence of 5/100,000 in the European Union (EU) [1]. As patients with nmDMD account for about 13% of the whole DMD patient population, it is estimated that approximately 2400 patients have nmDMD in the EU. There is no cure available and the current management of the disease is based on prevention and management of complications. Symptoms of muscle weakness are typically present from about three years of age. As the disease progresses, affected boys will typically need assisted ventilation in their late teens and die due to respiratory complications or heart failure in the 2nd–4th decade of life [2–4].

Ataluren targets the ribosomal translational machinery. It enables read-through of premature stop codons created by nonsense mutations in the mRNA of nmDMD patients, and hence expression of a full-length functional dystrophin protein (Fig. 1).

The applicant company PTC Therapeutics Ltd. submitted an initial marketing authorisation application for ataluren (Translarna©) to the European Medicines Agency for the treatment of nmDMD, in patients aged 5 years and older.

The demonstration of clinical benefit for ataluren was based on a single, phase 2b randomised, double-blind, placebo-controlled trial (PTC124-GD-007-DMD) comparing the efficacy and safety of ataluren 10, 10, 20 mg/kg TID and ataluren 20, 20, 40 mg/kg TID vs. placebo, in male patients ≥5 years of age who had a genetically confirmed nonsense mutation in the dystrophin gene. The review was conducted by the Committee for Human Medicinal Products (CHMP) of the EMA. Although the efficacy data available lacked robustness, the beneficial effects of ataluren were considered plausible and clinically relevant for this rare disease with high unmet medical need. The observed safety profile of ataluren was overall comparable to that of placebo.

A conditional marketing authorisation, subject to the completion of an ongoing confirmatory study, was granted in the EU on 5th August 2014 for the treatment of DMD resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older.

This paper summarises the scientific review of the application leading to the conditional approval in the EU, with a focus on the main issues discussed as part of this review. The detailed scientific assessment report and product information, including the summary of product characteristics (SmPC), are available on the EMA website (http://www.ema.europa.eu).

Disclaimer: This publication is a summary of the European Public Assessment Report and the summary of product characteristics available on the EMA website, focusing on the main issues discussed during the scientific evaluation. Healthcare professionals and interested readers are referred to the EMA website for up-to-date information on this marketing authorisation (http://www.ema.europa.eu). Serge Bakchine is the Chair of the EMA Scientific Advisory Group on Neurology and did not participate in the CHMP review of ataluren. The authors remain solely responsible for the opinions expressed in this publication.

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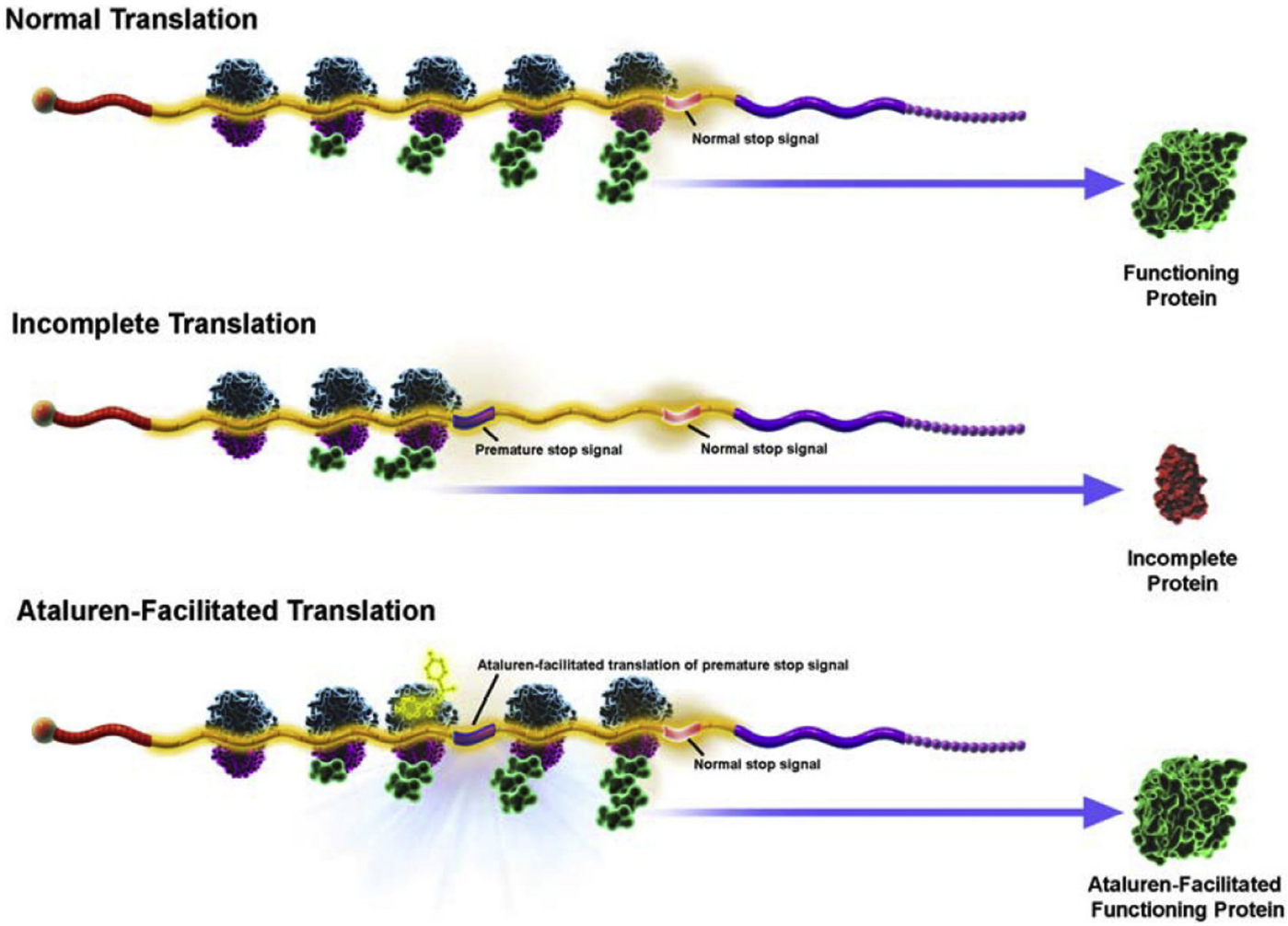

Fig. 1. Ilustrates ataluren's mechanism of action, described as promotion of the production of a functional dystrophin protein by enabling read-through of the premature stop codon associated with a nonsense mutation. Ataluren functions at the level of translation; it does not interfere with transcription or mRNA stability and does not alter levels of mRNA with premature stop codons or wild type mRNA.

2. Non-clinical aspects

Ataluren's mechanism of action was described as promotion of the production of a functional protein by enabling read-through of the premature stop codon associated with a nonsense mutation. Ataluren functions at the level of translation; it does not interfere with transcription or mRNA stability and does not alter levels of mRNA with premature stop codons or wild type mRNA. Ataluren does not enable read-through across premature stop codons due to frameshift mutations (insertions or deletions) or of mRNAs harbouring multiple sequential premature stop codons. Specific studies were conducted to demonstrate ataluren's selectivity for premature stop codons and the absence of promotion of read-through of normal stop codons.

The non-clinical studies performed in support of the claimed mechanism of action included *in vitro* experiments in different cellular preparations engineered to have premature stop codons, as well as myotubes from mdx mice, the mouse model of nmDMD, and myotubes derived from biopsies of nmDMD patients. Data were also collected in several *in vivo* nonsense mutation mouse models for nmDMD, nmCF (nmCF = nonsense mutation cystic fibrosis) and nmHurler syndrome. The non-clinical data available were considered sufficient to support the proposed mechanism of action and to alleviate earlier concerns on the selectivity of ataluren for premature stop codons.

An inverse dose–response relationship was seen during clinical development, where improved walking abilities were observed in the main trial in patients receiving ataluren 10, 10, 20 mg/kg/day compared to those receiving ataluren 20, 20, 40 mg/kg/day. This was attributed to a bell-shaped dose response of ataluren. Non-clinical data from cell cultures using myotubes from mdx mice and nmDMD patients, embryonic fibroblasts from a mouse model of nmHurler syndrome, and from a zebrafish model of nmDMD *in vivo* supported this hypothesis, although a bell-shaped dose response was not confirmed in mdx mice due to the limited number of tested ataluren doses.