Trabalhos Científicos

Título: Overview Of Clinical Trial Results In Nonsense Mutation Duchenne Muscular Dystrophy.

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Resumo: Introduction: Duchenne Muscular Dystrophy (DMD) is a rare genetic disorder which causes progressive functional decline. Objective: Provide an overview of clinical trial results in patients with nonsense mutation Duchenne muscular dystrophy (nmDMD) treated with ataluren, a ribosomal readthrough of a premature stop codon to produce full-length functional dystrophin. Methods: Phase 2 and 3 clinical trials of ataluren in nmDMD were reviewed, with efficacy and safety/tolerability findings summarized. Results: Clinical trials in nmDMD include: a Phase 2a proof-of-concept study (N=38) whose primary endpoint was muscle dystrophin expression following 28 days of treatment; a Phase 2b randomized controlled trial (RCT) (N=174), whose primary endpoint was change in six-minute walk distance (6MWD) over 48 weeks; an ongoing US-based open-label extension study (N=108) evaluating long-term safety; an ongoing non-US-based open-label extension study (N=94) evaluating long-term safety and efficacy; and a Phase 3 RCT, ACT DMD (N=228), whose primary endpoint was change in 6MWD over 48 weeks. The proof-of-concept study demonstrated increases in dystrophin production in post-treatment muscle biopsies from treated patients with nmDMD. The Phase 2b results demonstrated treatment effect of ataluren in 6MWD, timed function tests, and other measures of physical functioning, with larger treatment effects observed in patients at higher risk of ambulatory decline. The Phase 3 ACT DMD results demonstrated an treatment effect in patients with nmDMD in both primary and secondary endpoints, particularly in those with a baseline 6MWD of 300?400m. Ataluren was consistently well-tolerated in all three trials, as well as in the ongoing extension studies. Conclusions: The totality of the results demonstrates that the treatment with ataluren enables nonsense mutation readthrough in the dystrophin mRNA, producing functional dystrophin and slowing disease progression in patients with nmDMD.