MSG 2009 Abstract

Use of the 6-Minute Walk Test to Assess Potential Drug Effects of Ataluren (PTC124™) in Duchenne/Becker Muscular Dystrophy

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Introduction: Ataluren is being developed as a treatment for nonsense mutation Duchenne/Becker muscular dystrophy (nmDMD/BMD), a genetic disorder with high unmet need. Timed function tests (TFTs) are well accepted and commonly employed to assess disease progression in DMD/BMD; however, statistically significant changes in TFTs may not represent clinically significant changes in how patients actually function in their day-to-day lives. 6-minute walk distance (6MWD) has the potential to assess functional capacity in DMD/BMD, given that walking abnormalities are a major disease manifestation.

Methods: A Phase 2b controlled study is assessing 48 weeks of ataluren treatment in patients with nmDMD/BMD. Screening and baseline evaluations (~6 weeks apart) included 6MWD and TFTs (10-meter walk/run, 4-stair climb, 4-stair descent, stand from supine). Separately, an observational study evaluated change in 6MWD over ~1 year in boys with DMD and healthy boys.

Results: Pretreatment data from the Phase 2b study are available for 174 patients (median [range] age = 8 [5–20] years, height = 123 [97–174] cm, weight = 27 [15–80] kg, corticosteroid usage = 123/174 [71%]). Mean [SD] 6MWD was 357 [93] m at screening and 356 [96] m at baseline. The median [range] between-test interval was 42 [0–91] days. 6MWD test-retest reliability was high (r=0.91). 6MWD correlated with TFTs (range r=-0.79–-0.67). As expected, younger age and use of steroids predicted for improved 6MWD. Data from the observational study are available for 13 boys with DMD (median [range] age = 9 [5-12] years, height = 139 [109-165] cm, weight = 40 [18–72] kg, corticosteroid usage = 8 [62%]) and 16 age-matched healthy boys. Over ~1 year, 6MWD decreased in 10/13 (77%) boys with DMD (median [range] from 350 [125-481] m to 303 [0-530] m) and increased in 11/16 (69%) healthy boys (from 628 [479-754] m to 632 [590-724] m).

Conclusions: 6MWD is reproducible in nmDMD/BMD and correlates with factors known to predict disease severity. Most boys with DMD experience declines in ambulation over 1 year, with changes divergent from those in healthy boys. Slowing or stabilizing loss of ambulation with 48 weeks of ataluren would yield an important benefit.

Financial sponsor: PTC Therapeutics

L Atkinson, A Reha, GL Elfring, and LL Miller are employees of PTC Therapeutics and hold financial interests in the company.