A phase 2 randomized, placebo-controlled, multiple ascending-dose study of ACE-031 (ActRIIB-IgG1) in Duchenne muscular dystrophy (DMD): Preliminary results

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To evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamic (PD) effects of ACE-031 in boys with DMD. DMD is caused by dystrophin deficiency resulting in progressive muscle weakness. ACE-031 is a fusion protein comprised of the extracellular domain of activin receptor type IIB (ActRIIB) and IgG1 Fc domain, which inhibits myostatin and related proteins that negatively regulate muscle mass. In phase 1 studies in healthy adults, ACE-031 treatment resulted in increased mean muscle mass and decreased mean fat mass. Ambulatory, steroid-treated studies in healthy adults, ACE-031 treatment resulted in increased mean muscle mass and decreased mean fat mass. Ambulatory, steroid-treated DMD boys, age ≥ 4 years, were randomized to escalating doses of ACE-031 or placebo (3:1) for 12 weeks, with 12 weeks follow-up. The primary objective of the study was to assess safety and tolerability. PD endpoints included lean, fat, and bone mass (DXA), thigh muscle and fat mass and decreased mean fat mass. Changes in 6MWD from baseline to Week 48 (Study 007) or Week 12 (Study 007e) were determined for each group. High-dose treated subjects in Studies 007 and 007e with low concentrations experienced less mean decline in 6MWD over 48 or 12 weeks than high-concentration subjects (Study 007, low (N = 22, −11 m), high (N = 37, −60 m); Study 007e, low (N = 66, −5 m), high (n = 73, −17 m)). Among placebo-treated subjects in Study 007 who were first exposed to ataluren in Study 007e, low-concentration subjects experienced less mean decline in 6MWD over 12 weeks (N = 21, −2 m) than high-concentration subjects (N = 26, −12 m). Clinical trials in nonsense mutation dystrophinopathy support the inverse relationship between ataluren plasma concentration and 6MWD changes. These data show that ataluren activity was achieved at concentrations observed with the lower dose (10, 10, 20 mg/kg) in Study 007.

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The relationship of ataluren plasma concentration and response against clinical studies in nonsense mutation dystrophinopathy

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In a Phase 2b randomized, double-blind, placebo-controlled trial (Study 007) in nonsense mutation dystrophinopathy, low-dose ataluren (10, 10, 20 mg/kg TID) demonstrated a 29.7 m better mean change in 6-min walk distance (6MWD) from baseline to Week 48 vs placebo. No difference was observed for high-dose ataluren (20, 20, 40 mg/kg TID) vs placebo. In vitro experiments with ataluren demonstrated a bell-shaped concentration response curve. Study 007 and Study 007e (extension of Study 007; open-label high-dose) included measurements of 6MWD and ataluren trough plasma concentration. High-dose treated subjects within each study were grouped by mean trough concentration (≤10.0 μg/mL [low-concentration] vs >10.0 μg/mL [high-concentration]). 10.0 μg/mL was chosen as the cut-off value, consistent with nonclinical target plasma concentration (2–10 μg/mL) and with the finding that nearly all low-dose subjects in Study 007 had mean trough concentration ≤10.0 μg/mL. Changes in 6MWD from baseline to Week 48 (Study 007) or Week 12 (Study 007e) were determined for each group. High-dose treated subjects in Studies 007 and 007e with low concentrations experienced less mean decline in 6MWD over 48 or 12 weeks than high-concentration subjects (Study 007, low (N = 22, −11 m), high (N = 37, −60 m); Study 007e, low (N = 66, −5 m), high (n = 73, −17 m)). Among placebo-treated subjects in Study 007 who were first exposed to ataluren in Study 007e, low-concentration subjects experienced less mean decline in 6MWD over 12 weeks (N = 21, −2 m) than high-concentration subjects (N = 26, −12 m). Clinical trials in nonsense mutation dystrophinopathy support the inverse relationship between ataluren plasma concentration and 6MWD changes. These data show that ataluren activity was achieved at concentrations observed with the lower dose (10, 10, 20 mg/kg) in Study 007.

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