Ataluren confirmatory trial in DMD: Effect of Ataluren on activities of daily living in Nonsense Mutation Duchenne Muscular Dystrophy (nmDMD)

Background: Ataluren is the first drug to target the underlying cause of nmDMD, by promoting readthrough of a premature stop codon to produce full-length functional dystrophin.

Methods: ACT DMD was a randomized, double-blind, placebo-controlled Phase 3 study of ataluren 40 mg/kg/day, administered over 3 doses, vs placebo over 48 weeks. Inclusion/exclusion criteria were designed to enrich for a population with the greatest opportunity to detect a clinical benefit over a 48-week study, while being inclusive enough to enroll an appropriate number of subjects over a feasible time period for an orphan disease. Participants, 7-16 year-old boys, had a screening six-minute walk distance (6MWD) ≥150m and <80%-predicted. Patients or parents/caregivers reported changes from baseline in disease symptoms and activities of daily living (ADLs), rated on a Likert scale from 1 (much worse) to 5 (much better), using a DMD-specific survey developed for this study.

Results: Patients were randomized to ataluren (n=115) or placebo (n=115). Changes in ADL/disease symptoms trended in favor of ataluren across all physical functioning categories, including lower- and upper-extremity muscle function. At Week 48, more ataluren- than placebo-treated patients reported improvement (22.2% vs 16.1%, respectively) or lack of progression (55.6% vs 50.9%) in walking and fewer ataluren-treated patients reported worsening in walking (22.2% vs 33.0%). Effects did not reach significance. The same pattern of changes (with smaller differences) was observed for stair-climbing and upper-extremity activities of self-care.

Conclusions: Results indicate a positive clinical effect of ataluren on ADLs in boys with nmDMD, expanding the benefit beyond ambulation.

Study Supported By: PTC Therapeutics Inc.

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ICNC-0710 Results of North Star Ambulatory Assessments in the phase 3 ataluren confirmatory trial in patients with Nonsense Mutation Duchenne Muscular Dystrophy (ACT DMD)

Background: Results of the Phase 3, randomized, double-blind, placebo-controlled ACT DMD trial have been reported. The North Star Ambulatory Assessment (NSAA) is a validated functional scale to measure disease progression specifically in ambulant boys with Duchenne muscular dystrophy (DMD).

Methods: ACT DMD enrolled males aged 7–16 years with nonsense mutation (nm) DMD and baseline six-minute walk distance (6MWD) ≥150m and ≤80%-predicted. Eligible patients were randomized 1:1 to receive ataluren 10, 10, 20 mg/kg or placebo orally three-times daily for 48 weeks. A subgroup analysis of patients with baseline 6MWD of 300–400m was pre-specified. The NSAA consists of 17 activities ranging from standing from a chair to jumping.

Results: Of the 228 patients in the intent-to-treat population (ataluren, n=114; placebo, n=114), those who received ataluren gained a 1.5-point advantage in NSAA observed score compared with placebo (mean NSAA scores, ataluren: -7.0; placebo: -8.5; p=0.270). In the pre-specified subgroup of 99 patients with baseline 6MWD 300–400m, the advantage conferred by ataluren over placebo increased to 4.5 points (mean observed NSAA scores, ataluren: -5.7; placebo: -10.2; p=0.030).

Conclusions: Ataluren is the first drug to demonstrate a benefit to patients with nmDMD compared with placebo as assessed by NSAA scores; this benefit was especially pronounced in the subgroup with baseline 6MWD 300–400m. NSAA results when combined with 6MWD results, provide complementary information on different aspects of motor function in nmDMD patients and further demonstrate the efficacy of ataluren in this population. More detailed analysis of NSAA domains will be presented.

Study Supported By: PTC Therapeutics Inc.

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ICNC-0744 Eteplirsen, a Phosphorodiamidate Morpholino Oligomer (PMO) for Duchenne Muscular Dystrophy (DMD): Clinical update and longitudinal comparison to external controls on six-minute walk test (6MWT)

OBJECTIVE:
DMD, a rare, degenerative, X-linked genetic disease results in progressive muscle loss and premature death, occurring in ~1:3500-5000 males worldwide. DMD is primarily caused by frameshift-causing whole-exon mRNA deletions that prevent production of dystrophin protein. Eteplirsen, a PMO, is designed to induce production of internally-shortened dystrophin in patients amenable to exon 51-skipping.

METHODS:
An analysis of 6MWT performance over 3 years compared boys treated with 30/50 mg/kg eteplirsen weekly IV (N=12) versus a cohort of comparable external controls (EC, N=13) defined based on age, corticosteroid use, and genotype. Muscle biopsies of eteplirsen-treated boys were analyzed for exon skipping and dystrophin expression.

RESULTS:
At Year 3, a statistically significant treatment benefit of 151 meters on 6MWT was observed in eteplirsen-treated patients compared with EC (p<0.01). 2/12 (16.6%) eteplirsen patients lost ambulation by Year 1 with no additional losses observed, compared with 6/13 (46%) EC at Year 3.

Muscle biopsy analysis demonstrated exon 51-skipping in consented eteplirsen-treated patients (N=11) by RT-PCR and statistically significant increases (p<0.001) of dystrophin intensity and % dystrophin-positive fibers by immunohistochemistry over untreated DMD controls (N=9). Western blot confirmed dystrophin production in 9/11 patients.

No deaths, discontinuations due to AEs, or treatment-related SAEs were reported. LVEF on ECHO was stable over 3 years. AEs were generally mild and unrelated to study-drug.

CONCLUSIONS:
After 3 years of eteplirsen-treatment, DMD patients had a mean 6MWT that was 151m longer (p<0.01) than the comparable external cohort. Correct mRNA and de novo dystrophin were detected using 3 complementary methods in nearly all eteplirsen-treated patients.

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Development of a prognostic model for 1-year change in 6-minute walk distance (6MWD) in patients with Duchenne Muscular Dystrophy (DMD)

Introduction. Heterogeneous rates of disease progression in DMD, and resulting variation in outcomes, can complicate clinical trial design and cloud interpretation of results. To help explain variation in 6MWD, we developed and compared prognostic models for 1-year changes in this outcome.

Methods. Natural history data were collected from DMD patients at routine follow up visits approximately every 6 months over the course of 2 to 5 years. Patient demographics, treatment experience and ambulatory outcomes were recorded at each visit. Annualized changes in 6MWD were studied between all pairs of visits separated by ~1 year (8-16 months). Prediction models were developed using multivariable regression for repeated measures, and were evaluated using cross-validation.

Results. A total of n=171 ~1-year follow-up intervals from n=37 boys were included. Mean age was 9.4 years and mean 6MWD was 350.7 meters at the start of these intervals; 86% had received steroids. Predictions based on age, baseline 6MWD and steroid use explained 26% of variation in annualized 6MWD changes (R-squared = 0.26). A broadened prognostic model, adding timed 10-meter walk/run, 4-stair climb and rise from supine, as well as height and weight, significantly improved prediction, explaining 61% of variation in annualized 6MWD changes after cross-validation (R-squared=0.61).

Conclusion. A prognostic model incorporating timed function tests explained more than twice as much variation in 1-year changes in 6MWD compared to predictions based only on age, baseline 6MWD and steroid use. Such broader prognostic models have significant potential to inform clinical trial design and interpretation in DMD.

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ICNC-0757  Retrospective review of cause of death in Duchenne muscular dystrophy in the North East of England in the last 10 years

Introduction Duchenne muscular dystrophy (DMD) is the most common inherited muscle disease in children. Recent years have seen an increase in age of survival into adulthood following the introduction of proactive standards of care. However, young deaths in DMD are still reported. We have therefore analysed the age and cause of death in our DMD population, in particular unexpected deaths, in order to identify any risk factors for a young death. Methods Retrospective case note review of all deaths in the DMD population over the last 10 years in the North East. We divided the patients (deaths) into two groups according to their cardiorespiratory function prior to death. Result. 21 deaths occurred over the study period. Group 1 (n=17) are the patients who died of severe progressive cardiorespiratory failure. Group 2 (n=4) are patients who died suddenly in their teenage years due to various causes. Across both groups we identified concerns around nutrition, non-attendance at appointments, communication between care providers and psychological wellbeing. In addition, in the young deaths in group 2, fat embolism and/or adrenal suppression were considered to be possible contributing factors. Conclusion The main cause of death in DMD in our population remains a combination of cardiac and respiratory failure. There were however four cases of young and sudden deaths, we have highlighted potential areas of concern. By addressing these in detail we hope we can continue to improve clinical care and minimise the risk of an untimely death in DMD.

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Introduction: Pediatric myasthenia gravis (MG) can be congenital (Congenital myasthenic syndromes; CMS) or acquired. The diagnosis of juvenile MG (JMG) is based on clinical findings with supportive laboratory data.

Methods: Patients with JMG presenting to the pediatric neurology department from 2005 to 2015 in an Indian tertiary care hospital were included. Demographic data, investigations, treatment details, history of crises, thymectomy and outcome were studied.

Results: Total 19 patients (10 females and 9 males) were diagnosed as MG; four had CMS and 15 had acquired disease. Average age at onset was 3.7 years in latter group. Ocular presentation was seen in 6 (40%), oculo-bulbar symptoms in 1 and generalized in 8 (53%). Two patients with ocular presentation later had generalized symptoms. Nine (9/14) (60%) were anti-Acetylcholinesterase antibody positive, 1 was anti-MuSk positive and 5 were antibody negative. Average follow up was 3 years for 12 patients. Five were in remission and off all treatment, 3 were in remission on drugs and 5 were symptomatic on treatment at the end of follow up. Four patients with thymoma or thymic hyperplasia on radiology underwent thymectomy. All received pulse steroids and IVlg before surgery. One attained remission, one transient benefit and one did not benefit. One patient died due to complications of thymectomy.

Conclusion: We found a relatively higher rate of generalized symptoms. Outcomes are not uniformly favourable. No correlation between serology, severity of disease and thymic pathology was found. Treatment guidelines and role of thymectomy in JMG remain to be standardized.

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Asymptomatic or oligosymptomatic hyperckemia in pediatric patients

INTRODUCTION
Asymptomatic hyperCKemia (CK) requires extensive evaluation to determine the underlying cause. The aim of this study is to analyze the causes of asymptomatic or oligosymptomatic hyperckemia, to help in the long term follow up and prevention of possible complications.

METHODS
Retrospective study. Inclusion criteria: Patients under 18 years with CK levels ≥ 1.5 times normal in two separate controls separated by at least a month. Asymptomatic or oligosymptomatic forms including myalgia, fatigue, cramps or muscle stiffness. Testing performed: a) In all cases: manual test of muscle strength, cardiologic evaluation and familial CK levels. b) According to the case: Dystrophin MLPA, EMG, metabolic studies, acid alpha-glucosidase, studies for McArdle disease, MRI and / or muscle biopsy.

RESULTS
1) n = 26 patients, 4-18 years of age. 16 males. 19 asymptomatic, 7 oligosymptomatic. CK between 400 and 5900 IU / L. Follow-up: 2-5 years. 2) 61.5% (16) had family history of Dystrophinopathy, cramps and fatigue. 3) Diagnosis was obtained in 18 cases (69%): 6 dystrophinopathy, 3 CPT II, 3 organic acidurias, 1 dysferlinopathy, 1 RYR-1, 1 McArdle, 1 statin myopathy, 1 mitochondrial myopathy and 1 muscular dystrophy. 4) In the 8 patients without diagnosis, they had normal EMG, 3 with non-specific changes in biopsy. They remained asymptomatic but with high CK.

CONCLUSIONS
In our patients most cases of asymptomatic/oligosymptomatic hyperckemia were due to dystrophinopathies or metabolic disorders. We were unable to establish a correlation between CK blood levels and diagnosis. Most patients remained asymptomatic without clinical changes during the follow up time.

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