Background & Objectives

- DMD is a rare, X-linked recessive genetic disorder that causes severe and progressive muscle wasting characterized by a rapid physical functioning decline in childhood.
- Patients are mostly diagnosed at approximately five years of age, become wheelchair-bound by the age of 12 years if untreated, and die in their late teens or early 20s.
- Slowing ambulatory decline and delaying the point at which more rapid decline or complete loss of ambulation (LoA) occurs may alleviate patient disease burden; further, age at LoA is correlated with lung function decline and survival.
- The objectives of this research is to portray disease burden and treatment landscape in the United States (US) associated with DMD, and depict the evolving evidence associated with currently available treatment options to manage patient burden.

Methods

- A targeted review of data from published studies (2010-2017), recent scientific conferences, and DMD product package inserts was undertaken.
- An analysis of the placebo-arm of the phase 3 Ataluren Confirmatory Trial in DMD (ACT DMD) was also undertaken.
- ACT DMD was conducted in ambulatory male patients (N=230) with nonsense mutation DMD (nmDMD) ≥7 years old receiving corticosteroids at baseline for at least 6 months. Eighty-five percent of the patients in the study had baseline 6MWD ≥150m and ≥60% predicted, who were randomized 1:1 to receive ataluren 40mg/kg or placebo.
- The primary endpoint of ACT DMD was change from baseline to week 48 in 6 minute walk distance (6MWD), a validated clinical endpoint measuring global function and endurance.
- Key secondary endpoints included physical function (Timed Function Tests (TFTs), North Star Ambulatory Assessment (NSAA)) and health related quality of life (HRQoL).

Efficacy and Safety of Eteplirsen

- Eteplirsen increased dystrophin in the muscles of some patients treated with the drug, and reduction was associated with disease progression in some patients.
- The extrapolation of change in 6MWD (using the linear model) produced a mean age at LoA of 13.8 years for prednisone/prednisolone, and 17.6 years for eteplirsen, the difference equated to an incremental delay in LoA by 3.8 years attributable to deflazacort.

Results

- Treatment guidelines recommend oral corticosteroids (namely, deflazacort and prednisone) as the Standard of Care, with varying degrees of benefit-risk profiles.
- There is no cure for DMD, but pharmacological interventions, in addition to activities that can be effective in slowing muscle strength and functional decline.
- The treatment landscape of DMD is evolving with newly approved medications and 10 drug candidates with different mechanisms of actions under development.
- In Sept 2016, eteplirsen (Exondys 51®) was approved by the Food and Drug Administration (FDA) for treatment of patients with DMD gene deletions amenable to skipping of exon 51.
- In Feb 2017, deflazacort (Emflaza®) was approved by the FDA as the first corticosteroid for the treatment of all DMD patients 25 years or older.

Efficacy and Safety of Deflazacort

- Deflazacort was also shown to improve muscle strength and pulmonary function in non-ambulatory boys.
- Most frequent TEAEs observed include:
  - Rash
  - Urinary frequency
  - Urticaria
  - Increased liver enzymes

New Analyses (post-hoc) of the ACT DMD Placebo Arm

- Patient characteristics did not differ significantly at baseline.
- Mean (overall deflazacort, prednisone/prednisolone) age of 9.0 (9.2, 8.9), BMI (kg/m²) of 18.8 (18.6, 18.9) and 6MWD (m) of 362.7 (361.3, 363.9).

Results (continued)

- Percent exposed to a corticosteroid ≥212 months prior to randomization: 83.5% (deflazacort: 86.8%, prednisone/prednisolone: 80.6%).
- With ACT DMD, there are ≥5 observed include:
  - Deflazacort, prednisone/prednisolone:
    - Nasopharyngitis (11%, 27%), headache (19%, 18%), vomiting (19%, 17%), diarrhea (15%, 19%), back pain (14%, 10%), and nasopharyngitis, among deflazacort vs. prednisone cohorts vs. placebo; patients taking deflazacort had significantly less weight gain than prednisone at week 52.

CONCLUSION

- DMD imposes a significant burden among DMD patients due to lack of ambulation at an early age, lowered HRQoL and a shorter life span.
- Treatment guidelines in the US recommend corticosteroids as standard of care therapies to manage DMD.
- Eteplirsen and deflazacort are now available in the US to manage DMD and alleviate disease burden.
- Results from the new post-hoc analysis of ACT DMD data suggest that deflazacort has a significant benefit vs. prednisone/prednisolone in multiple measures of disease progression.

References

12. PTI Therapeutics - Available from: https://www.ptitherapeutics.com/