Pulmonary Function Is Stable Through Week 144 in Patients With Duchenne Muscular Dystrophy (DMD) Treated With Exon-Skipping Drug Eteplirsen in Phase IIb Study

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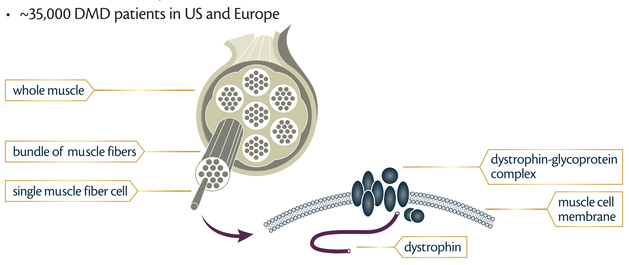
PMO

INTRODUCTION

Duchenne Muscular Dystrophy (DMD): Devastating Rare Disease

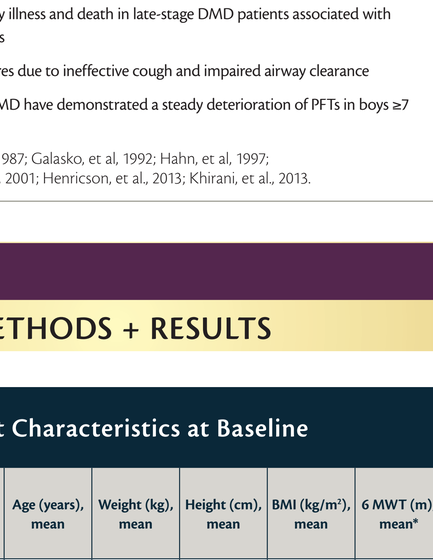
- Rare X-linked recessive degenerative neuromuscular disease
- DMD is caused by mutations in the gene coding for dystrophin, a protein that plays a key structural role in muscle fiber function
- Lack of dystrophin results in severe progressive muscle loss leading to eventual loss of ambulation and premature death often due to respiratory or cardiac failure
- Affects ~1 in 3,500 boys worldwide*
- ~35,000 DMD patients in US and Europe



*Prevalence of Duchenne/Becker Muscular Dystrophy Among Males Aged 5–24 Years—Four States, 2007. *MMWR*. 58(40);1119-1122; Emery 1991.

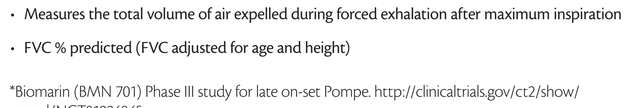
Eteplirsen: RNA Modulator That Addresses the Underlying Cause of DMD

- Directs alternative splicing by skipping of exon 51 in dystrophin pre-mRNA
- Systemic administration through weekly IV infusion
- Charge-neutral PMO chemistry
- Plasma half-life of 2 to 6 hours
- Cleared through the kidney
- >1,800 doses at up to 50 mg/kg/wk given to boys with DMD for nearly 3 years without clinically significant treatment-related adverse events

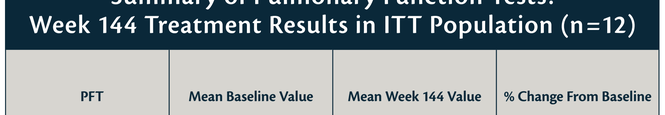


Exon-Skipping Approach: Repair mRNA to Restore Protein Translation & Dystrophin Production

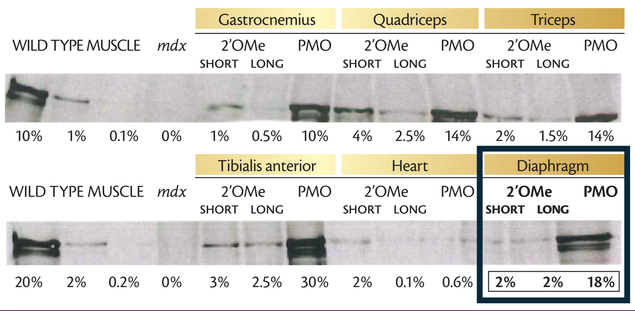
EXAMPLE OF ETEPLIRSEN-AMENABLE GENOTYPE: DELETION OF EXONS 49-50 RESULTS IN **AN OUT-OF-FRAME DELETION** IN mRNA



BY SKIPPING EXON 51, IN-FRAME **mRNA TRANSLATION IS RESTORED**, ENABLING THE PRODUCTION OF A FUNCTIONAL DYSTROPHIN PROTEIN



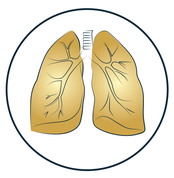
PMO Restores Dystrophin in Diaphragm: MDX Mouse Model



- **Significant increase of dystrophin expression achieved in diaphragm muscle of mdx mouse following a single 100-mg/kg dose of PMO**
- **PMO more active than same sequence with 2'OMe backbone**

Heemskerk et al, 2009.

Pulmonary Function Tests: Importance for DMD



PULMONARY FUNCTION TESTS

- Decreases in pulmonary function are a strong predictor of subsequent mortality
- DMD natural history studies show that pulmonary function tests offer sensitive measurement of respiratory muscle strength

RESPIRATORY FUNCTION DECLINE IN DMD

- High incidence of respiratory illness and death in late-stage DMD patients associated with progressive muscle weakness
- Majority of respiratory failures due to ineffective cough and impaired airway clearance
- Natural history studies in DMD have demonstrated a steady deterioration of PFTs in boys ≥7 years of age

Braverman, et al; Smith, et al, 1987; Galasko, et al, 1992; Hahn, et al, 1997; Kang, et al, 2000; Phillips, et al, 2001; Henricson, et al., 2013; Khirani, et al., 2013.

MIP, MEP, and FVC: Phase IIB Exploratory Efficacy Endpoints

MAXIMUM INSPIRATORY AND EXPIRATORY PRESSURE (MIP AND MEP)

- Highest level of pressure a person can generate during inhalation (MIP) and exhalation (MEP)
- MIP % predicted (adjusted for weight), MEP % predicted (adjusted for age)
- Declines in MIP and MEP correlate with decreases in voluntary cough capacity
- MEP typically deteriorates before MIP and FVC in DMD patients
- MIP and MEP % predicted included as primary and secondary clinical endpoints respectively in a Phase III study of another neuromuscular disease indication*

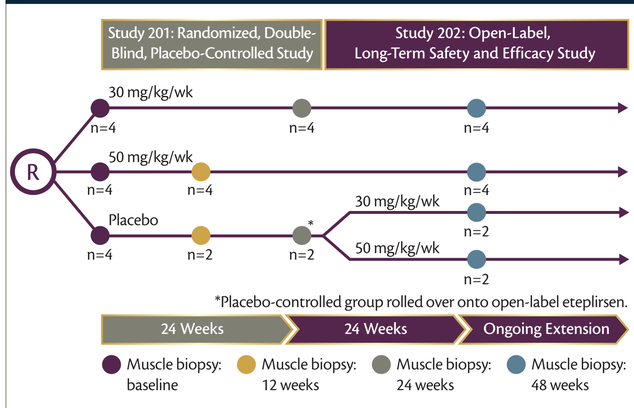
FORCED VITAL CAPACITY (FVC)

- Measures the total volume of air expelled during forced exhalation after maximum inspiration
- FVC % predicted (FVC adjusted for age and height)

*Biomarin (BMN 701) Phase III study for late on-set Pompe. http://clinicaltrials.gov/ct2/show/record/NCT01924845.

METHODS + RESULTS

Eteplirsen Phase IIB Studies



*Placebo-controlled group rolled over onto open-label eteplirsen.

KEY INCLUSION CRITERIA

- Male DMD, age 7-13 inclusive
- Out-of-frame deletion(s) amenable to correction by exon 51 skipping
- Stable dose of oral corticosteroids for at least 24 weeks prior to study entry
- Between 200 and 400 meters (±10% upon repeating) on 6MWT at baseline

Patient Characteristics at Baseline

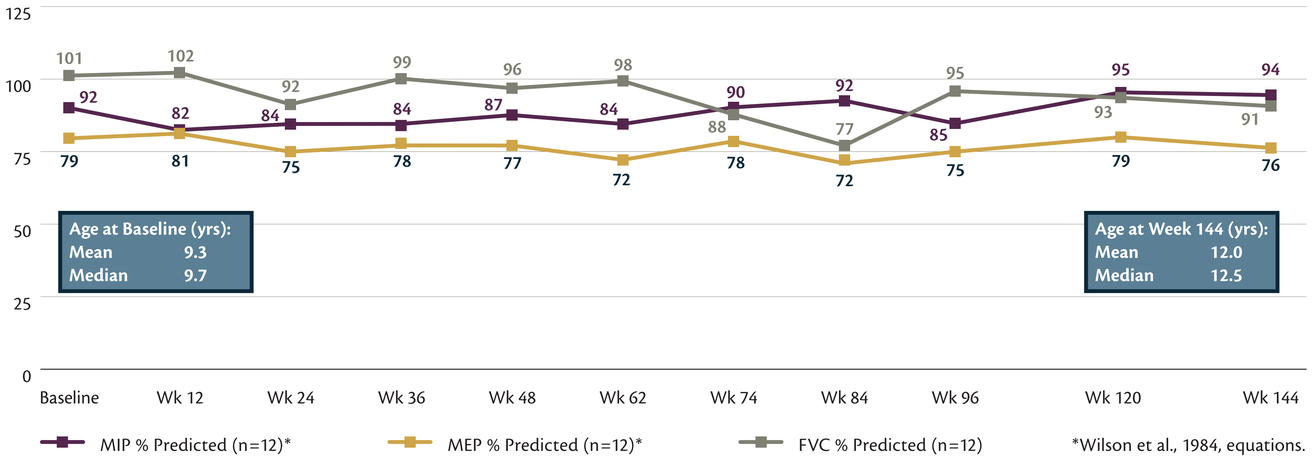
Cohort	N	Age (years), mean	Weight (kg), mean	Height (cm), mean	BMI (kg/m²), mean	6 MWT (m), mean*
PBO/Delayed-Tx	4	8.8	30.7	119.3	21.5	380.3
Eteplirsen (30 mg/kg)	4	9.8	34.9	130.5	20.3	347.3
Eteplirsen (50 mg/kg)	4	9.1	29.1	121.3	19.6	384.8
Total *(min, max)*	12	9.3 *(7.3, 11.0)*	31.5 *(22.1, 39.8)*	123.7 *(116, 138)*	20.5 *(16.4, 25.6)*	370.8 *(259, 437)*

*6MWT baseline values per patient were collected on 2 consecutive days, mean is based on average of both values.

Summary of Pulmonary Function Tests: Week 144 Treatment Results in ITT Population (n=12)

PFT	Mean Baseline Value	Mean Week 144 Value	% Change From Baseline
MIP	63.1 cm H_2O	72.4 cm H_2O	+14.7%
MEP	68.1 cm H_2O	76.8 cm H_2O	+12.8%
FVC	1.73 liters	1.92 liters	+11.0%
MIP % Predicted	91.7%	93.9%	+2.4%
MEP % Predicted	79.3%	75.7%	−4.5%
FVC % Predicted	101.3%	90.9%	−10.3%

MIP, MEP & FVC % Predicted to Week 144 Demonstrate Stability in Intent-to-Treat Population



*Wilson et al., 1984, equations.

CONCLUSIONS

- Eteplirsen demonstrated stability on PFTs in the ITT population (n=12), as measured by MIP, MEP, FVC, MIP % predicted, MEP % predicted and FVC % predicted from baseline through Week 144
- The reported stability on PFT measurements over nearly 3 years is contrary to a steady decline observed in the DMD natural history