Translarna™ (ataluren) for Duchenne Muscular Dystrophy

Peripheral and CNS Drug Advisory Committee (PCNSDAC)
Food and Drug Administration
September 28, 2017
Ataluren for Duchenne Muscular Dystrophy Caused by Nonsense Mutation (nmDMD)

Murad Husain
Senior Vice President
Global Regulatory Affairs
PTC Therapeutics
nmDMD is a Rare, Debilitating, Progressive, Fatal Genetic Disease

- Irreversible loss of muscle function and ambulation
- Premature death in the mid-20s
- ~1800 patients in the US, only ~700 are ambulatory
- No treatment options address cause of disease

Bladen et. al, 2015; Bushby et al., 2010a.
Meeting to Discuss Interpretability and Persuasiveness of Data as Evidence of Efficacy

- FDA review includes
  - Evidence of effectiveness and limitations of application
  - Requirement of p-value of < 0.05 required for approval
- FDA has shown flexibility in prior approvals
- Interpretation requires clinical context
  - Non-linear disease trajectory
  - Unmet Need
  - Rarity of disease
Ataluren Benefit-Risk is Positive

- Demonstrated production of dystrophin in patients
  - Dystrophin production used for prior accelerated approval
- Preservation of key milestones
  - Slowed muscle function decline: 6MWT, 4-stair climb, 4-stair descend, 10m walk/run
  - Delayed loss of individual muscle functions
  - Preservation of ambulation
  - Preservation of pulmonary function
- Safety profile is favorable
## Multiple Studies Provide Evidence of Ataluren Benefit

<table>
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<tr>
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### Enriched population required for 6MWT

### Pre-specified 300-400m subgroup

### Ongoing Studies
- Study 025o (Global Registry)
- Study 041 (Post-market Long-term RCT)

*Median exposure*
Real-World Ataluren Evidence

- Ataluren approved outside the US since 2014
- Available in > 25 countries
  - ~700 patient-years of exposure continues to support positive favorable safety profile
  - ~95% patient retention
- Global registry with real-world evidence generation ongoing
Proposed Ataluren Indication

- Treatment of dystrophinopathy resulting from a nonsense mutation in the dystrophin gene
<table>
<thead>
<tr>
<th>Agenda</th>
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<tr>
<td>Ataluren</td>
<td>Ellen Welch, PhD</td>
<td>Senior Vice President, Genetic Disorders &amp; Translational Medicine, Biology PTC Therapeutics</td>
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<td>Mechanism of Action</td>
<td></td>
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<td>DMD Natural History and Clinical Endpoints</td>
<td>Kevin Flanigan, MD</td>
<td>Director, Center for Gene Therapy Nationwide Children’s Hospital</td>
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<td>Ataluren Efficacy and Safety</td>
<td>Joe McIntosh, MD</td>
<td>Senior Vice President, Head of Clinical Development PTC Therapeutics</td>
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<td>Clinical Perspective</td>
<td>Craig McDonald, MD</td>
<td>Director, Neuromuscular Disease Clinics University of California, Davis Children’s Hospital Study Chair, CINRG Duchenne Natural History Study</td>
</tr>
</tbody>
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### Additional External Experts

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
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<tbody>
<tr>
<td>Christopher Rubino, PharmD</td>
<td>Executive VP, Pharmacometrics Institute for Clinical Pharmacodynamics</td>
</tr>
<tr>
<td>LJ Wei, PhD</td>
<td>Professor of Biostatistics Harvard University</td>
</tr>
</tbody>
</table>
Ataluren Dystrophin Production and Mechanism of Action

Ellen Welch, PhD
Senior Vice President
Genetic Disorders and Translational Medicine
PTC Therapeutics
Ataluren is Mechanism Based Treatment for Genetic Disorders Caused by Nonsense Mutation

Premature Stop Codon Interrupts Protein Synthesis

Ataluren Enables Readthrough at Premature Stop Codons

Ataluren Enables Readthrough at Premature Stop Codons

- Nonsense mutation must be present
- Mechanism of action and patient population distinct from exon skipping drugs

Bell-Shaped Concentration Response Observed

**Human Myotubes**

![Graph showing the bell-shaped concentration response of Dystrophin Expression Fold Increase ± SEM with Ataluren Concentration (μg/mL).]

**Mouse Myotubes**

![Graph showing the comparison of Dystrophin staining (arbitrary units) with Ataluren Concentration (μg/mL).]

Readthrough Activity Modulated by Ribosome Binding

Ribosomal readthrough reduced when both sites occupied

Ribosomal readthrough induced when high affinity site occupied
Multiple Lines of Evidence Support Full-Length Dystrophin Production

Normal mouse
No treatment

Tibialis anterior

Diaphragm

Heart

nmDMD mouse
No treatment

nmDMD mouse
Ataluren

Multiple Lines of Evidence Support Full-Length Dystrophin Production

- Spectrin staining used to define edges of myotubes
- Region of interest encompassed entire myotube (excluding nuclei)
- Compare ataluren-treated cultures to untreated cultures

Multiple Lines of Evidence Support Full-Length Dystrophin Production

- Spectrin staining used to define edges of myotubes
- Region of interest encompassed entire myotube (excluding nuclei)
- Compare ataluren-treated cultures to untreated cultures

Ataluren Enables Readthrough at Nonsense Codons to Produce Functional Protein

- Enables readthrough at premature stop codons
  - Readthrough of normal termination codons not observed
- Exhibits a bell-shaped concentration response
- > 40 publications confirm ataluren’s mechanism of action
Duchenne Muscular Dystrophy: Unmet Medical Need, Evolution of Natural History and Clinical Trial Challenges

Kevin Flanigan, MD
Director, Center for Gene Therapy
Nationwide Children’s Hospital
Professor of Pediatrics and Neurology
The Ohio State University
DMD is a Relentlessly Progressive, Fatal Childhood Genetic Disorder

- Characterized by decline in ambulatory function that rapidly accelerates once a transition threshold is reached
  - Stable ambulatory function in early years
  - Followed by non-linear, rapidly progressing decline
- Loss of ambulation early in teenage years
- Death due to respiratory and cardiac dysfunction
DMD Caused by Lack of Functional Dystrophin

- Dystrophin is an essential muscle cell protein
  - Protects muscle cells from load-induced damage
- Deficiency leads to damage to muscle cell membrane and irreversible loss of muscle fibers
- Loss of skeletal muscle fibers leads to rapid loss of function
- Treatment goal to help slow or stabilize disease progression
Dystrophin Production Leads to Clinical Benefit

- Commonly accepted that generation of functional dystrophin will predict benefit\(^1\)
- DMD studies support that small amounts of dystrophin provide benefit
- Dystrophin production used as basis for accelerated approval

1. FDA workshop, April 2015.
Methods to Confirm Existence of Dystrophin

- Immunofluorescence is reliable and reproducible method to detect dystrophin change\(^1,2\)
- Exact correlation between amount of dystrophin and clinical measures is still not defined

Young Boy (Assessment 2007)
Same Boy, 8 Years Later (Assessment 2015)
DMD Progression is Sequential, Non-Linear and Irreversible

- **Impaired Ability to Hop, Run, Jump, Rise**
- **Loss of Stair Climb**
- **Loss of Stair Descend**
- **Loss of Ambulation**
- **Loss of Upper Limb**
- **Ventilation**
- **Death**

**Early Physical Manifestations**

Loss of ambulation is predictive of late physical manifestations

**Late Physical Manifestations**
Natural History Studies Show Stability When \( 6\text{MWD} \geq 400\text{m} \)\(^1,2,3\)

Biological Plausibility of a 300 Meters 6MWD as Predictor of Accelerated Decline Phase

N=129; Sweeney, 2014 PPMD Annual Connect Conference.
Experts agree that DMD muscle function decline has 3 phases with progressive acceleration over time.

- **Baseline 6MWD**
- **Stable Phase**
- **Transition Phase**
- **Accelerated Decline Phase**

Most sensitive phase to assess changes in muscle decline within 48 weeks.

References:
- McDonald et al. Muscle & Nerve 2013;
- Goemans et al. Neuromuscular Disorders 2013;
- Pane et al. PLOS One 2014;
- GSK/Biomarin clinical trial data;
- Tadalafil clinical trial data;
- Sweeney et al., 2013;
FDA Statements Support Importance of Baseline 6MWD of 300-400 Meters

“…loss of ability to walk…often occurs with a sharp decline when 6MWT decreases below about 300m.”

FDA briefing document for eteplirsen advisory committee (1/2016)

“…subjects with baseline 6MWD of > 400m…are likely to have a slower decline.”

FDA briefing document for drisapersen advisory committee (11/2015)
Measuring DMD Progression Requires Use of Multiple Outcome Measures

**Endpoint Measures**

**Muscle Function**
- 6-minute walk test
- 4-stair climb
- 4-stair descend
- 10m walk / run

**Disease Progression**
- North Star Ambulatory Assessment (NSAA)
- Loss of Ambulation

**Pulmonary Function**
- Forced vital capacity
Use of NSAA has Evolved to Focus on Loss of Individual Muscle Functions

17 Measures
- Hop (left leg)
- Hop (right leg)
- Stand on heels
- Rise from floor
- Run
- Jump
- Lift head
- Descend box step (left leg)
- Descend box step (right leg)
- Climb box step (left leg)
- Climb box step (right leg)
- Stand (left leg)
- Stand (right leg)
- Get to sitting
- Rise from chair
- Walk
- Stand

NSAA Scoring

<table>
<thead>
<tr>
<th>Patient with Function</th>
<th>Complete Loss of Function</th>
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<tbody>
<tr>
<td>2 Perform</td>
<td>0 Unable to Perform</td>
</tr>
<tr>
<td>1 Perform with Difficulty</td>
<td></td>
</tr>
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CO-35
Natural History Cohort from UK Shows Significant Loss of Function in a 1-Year Period

NSAA UK (N=514)

Proportion of patients who lost function (%)
DMD is a Devastating, Relentlessly Progressive Disorder Resulting in Irreversible Muscle Loss

- Any change in dystrophin is important
- Difficult to study
  - Evaluate patients in Transition Phase
  - Use multiple endpoints
- Preservation of function is critical
Ataluren Clinical Efficacy

Joe McIntosh, MD
Senior Vice President
Head of Clinical Development
PTC Therapeutics
## Multiple Studies Provide Evidence of Ataluren Benefit

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*Median exposure
Multiple Sources Demonstrate Substantial Evidence of Ataluren Efficacy

- Production of dystrophin in patients
- Consistency of results across RCTs
  - Delay for key endpoints: 6MWT, 4-stair climb, 4-stair descend, 10m walk/run
  - Greater benefit seen in Transition Phase
- Consistent benefit among functional milestones
  - Delayed loss of individual muscle functions
  - Delayed loss of ambulation
  - Preservation of pulmonary function
Study 004: Designed to Assess Production of Dystrophin in nmDMD Patients

- Evaluation at Day 1
  - Ataluren 4,4,8 mg/kg
    (N=6)

- Ataluren 10,10,20 mg/kg
  (N=20)

- Ataluren 20,20,40 mg/kg
  (N=12)

- Evaluation at Day 28

28 Days

- Biopsy from entire extensor digitorum brevis
- Plasma samples at Day 1 and Day 28
- CK samples at Day 1, Day 28 and post follow-up

28 day Follow-up
### Study 004: Demonstrated Dystrophin Expression

<table>
<thead>
<tr>
<th>Patients</th>
<th>Mean % Dystrophin from Baseline</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=38</td>
<td>11.1%</td>
<td>3.02, 19.1</td>
</tr>
</tbody>
</table>

- Standard dystrophin quantification method used (immunohistochemistry)
- 61% of patients showed an increase in dystrophin
Study 004: Demonstrated Dystrophin Expression Based on Blinded Review

- Full-length dystrophin protein is produced
- Dystrophin is correctly localized

Bonnemann et al., WMS, 2007.
Study 004: Sample Size Insufficient to Discern Dose Response

Ataluren Concentration (µg/mL)
Day 28 Plasma 2 hour post dose

Dose Level (mg/kg/day)
- 4,4,8 mg/kg
- 10,10,20 mg/kg
- 20,20,40 mg/kg

N=6
N=20
N=12

19.3 µg/mL
Study 004 Relevance

- Demonstration of dystrophin production
- Regulatory precedent for approval based solely on small quantities of dystrophin
Multiple Sources Demonstrate Substantial Evidence of Ataluren Efficacy

- Production of dystrophin in patients
- Consistency of results across RCTs
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Study 007: First Randomized Placebo-Controlled Study in nmDMD

Eligibility Criteria
- ≥ 5 years of age
- Baseline 6MWD ≥ 75m

Randomization (1:1:1)

- Ataluren 10,10,20 mg/kg (N=57)
- Ataluren 20,20,40 mg/kg (N=60)
- Placebo (N=57)

Outcome Measures
- Primary endpoint: 6MWT
- Key secondary endpoints
  - 10-meter walk/run
  - 4-stair climb
  - 4-stair descend

48-weeks
(Examination every 6 weeks)
Study 007: Change in 6MWD at 48 Weeks (ITT)

Change in 6MWD
Mean ± SE (meters)

Ataluren 10,10,20 mg/kg (N=57)
LS Mean Δ = + 26.4m
Ataluren 20,20,40 mg/kg (N=60)
Placebo (N=57)

Time (weeks)

Rank transformed p = 0.149
Mixed-model repeated-measures analysis (MMRM)
Study 007: TFT Results Consistently in Favor of Ataluren 10,10,20 mg/kg

Ataluren (N=57)
Placebo (N=57)

Δ = 1.1s
Δ = 2.4s
Δ = 1.6s

Clinically Meaningful Change (1.0 - 1.5 seconds)

ITT
10m walk / run p=0.316, 4-stair climb p=0.041, 4-stair descend p=0.197
Study 020: Randomized Placebo-Controlled Study in Patients with nmDMD

Eligibility Criteria
- ≥ 7 to ≤ 16 years of age
- Steroid use ≥ 6 months
- Baseline 6MWD ≥ 150m
- Baseline 6MWD ≤ 80% predicted for age & height

Randomization (1:1)
- Ataluren 10,10,20 mg/kg (N=115)
- Placebo (N=115)

Outcome Measures
- Primary endpoint: 6MWT
- Key Secondary endpoints
  - 10-meter walk/run
  - 4-stair climb
  - 4-stair descend

48-weeks
(Examination every 8 weeks)
Study 020: Inclusion Criteria Did Not Enrich Transition Phase Population

Baseline 6MWD

Rapid Decline

Stable

100 m  200 m  300 m  400 m  500 m

Study 007 ITT

≥ 75 m  ≤ 533 m

356 m

Study 020 ITT

≥ 143 m  ≤ 526 m

364 m

≥ 300 m  < 400 m

Transition Phase*

*Study 020 pre-specified analysis
Study 020: Change in 6MWD Over 48 Weeks (ITT)

Change in 6MWD, Mean ± SE (meters)

Ataluren (N=114)
Placebo (N=114)

LS Mean Δ = 13.0 m

p=0.213
Study 020: TFT Results Consistently Support Ataluren Benefit

Ataluren (N=114)
Placebo (N=114)

Clinically Meaningful Change (1.0 - 1.5 seconds)

10m walk / run p=0.117, 4-stair climb p=0.058, 4-stair descend p=0.012
Positive Benefit Seen in Ataluren Treated Patients Across Muscle Function Outcomes

**Study 007**

- **Favors Placebo**
- **Favors Ataluren**

Δ 6MWD Change at Week 48, LS Mean 95% CI (m)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>-20</th>
<th>0</th>
<th>20</th>
<th>40</th>
<th>60</th>
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<tr>
<td>6MWD</td>
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<tr>
<td>4-stair descend</td>
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Δ TFT Change at Week 48, LS Mean 95% CI (s)

<table>
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<tr>
<th>Endpoint</th>
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<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
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**Study 020**

- **Favors Placebo**
- **Favors Ataluren**

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Δ TFT Change at Week 48, LS Mean 95% CI (s)

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Meta-analysis Provides Additional Evidence of Ataluren Benefit Across Endpoints

Δ 6MWD Change at Week 48, LS Mean 95% CI (m)

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<th>Favors Ataluren</th>
<th>LS Mean (95% CI)</th>
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<tr>
<td>6MWD</td>
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<td>17.2 (0.2, 34.1)</td>
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<tr>
<td>10-meter walk / run</td>
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<td>1.1 (-0.1, 2.2)</td>
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<td>4-stair climb</td>
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<td>1.7 (0.4, 2.9)</td>
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<tr>
<td>4-stair descend</td>
<td></td>
<td></td>
<td>1.9 (0.6, 3.2)</td>
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Δ TFT Change at Week 48, LS Mean 95% CI (s)

Study 007 ITT + Study 020 ITT (N = 342)
Assessing Studies 007 and 020 in Light of 6MWT Natural History

Baseline 6MWD

Stable Phase

Transition Phase

Accelerated Decline Phase

Most sensitive phase to assess changes in muscle decline within 48 weeks

## Patients with Baseline 6MWD of 300-400 Meters

<table>
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<tr>
<th>Prespecified Analyses for Baseline 6MWD</th>
<th>Study 007 (N=114)</th>
<th>Study 020* (N=228)</th>
</tr>
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<tbody>
<tr>
<td>≥ 400 meters</td>
<td>37%</td>
<td>37%</td>
</tr>
<tr>
<td>≥ 300 to &lt; 400 meters (Transition Phase)</td>
<td>39%</td>
<td>43%</td>
</tr>
<tr>
<td>&lt; 300 meters</td>
<td>24%</td>
<td>20%</td>
</tr>
</tbody>
</table>

*Prespecified in statistical analysis plan but not included in multiplicity adjusted analyses.
Consistent Benefit in 6MWD Seen in Patients with Baseline 300-400 Meters

\[ \Delta = 46 \text{ m} \]

\[ \Delta = 43 \text{ m} \]

Study 007  
300-400 m (n=44)

Study 020  
300-400 m (n=99)
Consistent TFT Benefit Seen in Patients with Baseline 6MWD 300-400 Meters

Study 007

- 10m walk / run
- 4-stair climb
- 4-stair descend

△ 2.7s  △ 3.3s  △ 4.0s

LS Mean (SE) Treatment Difference vs Placebo at Week 48 (seconds)

Study 020

- 10m walk / run
- 4-stair climb
- 4-stair descend

△ 1.8s  △ 3.5s  △ 4.4s

Clinically Meaningful Change (1.0 - 1.5 seconds)

Study 007 ITT
Ataluren 10,10,20 mg/kg (N=22) Placebo (N=22)
10 m walk / run p=0.100, 4-stair climb p=0.072, 4-stair descend p=0.042

Study 020 ITT
Ataluren (N=47) Placebo (N=52)
10 m walk / run p=0.066, 4-stair climb p=0.003, 4-stair descend p<0.001
Multiple Sources Demonstrate Substantial Evidence of Ataluren Efficacy

- Production of dystrophin in patients
- Consistency of results across RCTs
  - Delay for Key endpoints: 6MWT, 4-stair climb, 4-stair descend, 10m walk/run
  - Greater benefit seen in Transition Phase
- Consistent benefit among functional milestones
  - Delayed loss of individual muscle functions
  - Delayed loss of ambulation
  - Preservation of pulmonary function
Ataluren Benefit in Loss of Ambulation Studies 007 and 020

Loss of ambulation (%)

Baseline 6MWD ≥ 400 m

- Study 007: n=20
- Study 020: n=43

Baseline 6MWD = 300-400 m

- Study 007: n=22
- Study 020: n=47

Baseline 6MWD < 300 m

- Study 007: n=15
- Study 020: n=24

None

- Ataluren: 0%
- Placebo: 0%
Ability to Climb and Descend Stairs Preserved in Ataluren-Treated Patients

Loss of 4-stair climb

- **Study 007**
  - Ataluren: 19%
  - Placebo: 23%
  - N: 57

- **Study 020**
  - Ataluren: 11%
  - Placebo: 20%
  - N: 114

Loss of 4-stair descend

- **Study 007**
  - Ataluren: 16%
  - Placebo: 19%
  - N: 57

- **Study 020**
  - Ataluren: 11%
  - Placebo: 18%
  - N: 114
Study 020: Sequential Loss of Function Reported in NSAA Evaluation

- Hop (left leg)
- Hop (right leg)
- Stand on heels
- Rise from floor
- Run
- Jump
- Lifts head
- Descend box step (left leg)
- Descend box step (right leg)
- Climb box step (left leg)
- Climb box step (right leg)
- Stand (left leg)
- Stand (right leg)
- Get to sitting
- Rise from chair
- Walk
- Stand

% patients who lost function

Placebo (N=114)
Study 020: Preservation of Multiple Functions with Ataluren in NSAA

p=0.010, 31% in Risk Reduction in favor of ataluren
CINRG Study: Pulmonary Function (FVC) Begins to Decline at 12.5 Years

Breakpoints in slope with regard to age are indicated. 238 assessments from 114 patients included from the CINRG study;
Study 019: Extension Data Support Preservation in Pulmonary Function by 4 Years with Ataluren

Absolute FVC Change = 13.8%* compared to matched CINRG patients

Breakpoints in slope with regard to age are indicated. 238 assessments from 114 patients included from the CINRG study; 259 assessments from 54 patients included from study 019. Matched based on age and steroid use.

*p=0.005
Ataluren Data is Interpretable Evidence of Benefit in Patients with nmDMD

- Study 004 showed dystrophin production in patients
- Results of Studies 007 and 020 are interpretable in light of current understanding of natural history
  - Consistency in effect, including Meta-analysis
  - Large differences in baseline 300-400m 6MWD subgroup
- Key functions are preserved in ataluren-treated patients
  - NSAA functions
  - Ambulation, stair-climb and stair-descend
  - Pulmonary function
Ataluren Safety
# 445 Patients Exposed to Ataluren in DMD Clinical Studies

<table>
<thead>
<tr>
<th>Ataluren Exposure</th>
<th>DMD Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 dose</td>
<td>445</td>
</tr>
<tr>
<td>Completed DMD studies</td>
<td>333</td>
</tr>
<tr>
<td>&gt; 48 week</td>
<td>262</td>
</tr>
<tr>
<td>Open-label extensions</td>
<td>420</td>
</tr>
<tr>
<td>&gt; 48 week</td>
<td>389</td>
</tr>
</tbody>
</table>

As of July 31, 2016 submission cut off
## Similar AE Profile Between Ataluren and Placebo

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Study 007 Ataluren (N=57)</th>
<th>Study 007 Placebo (N=57)</th>
<th>Study 020 Ataluren (N=115)</th>
<th>Study 020 Placebo (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 AE</td>
<td>97%</td>
<td>98%</td>
<td>90%</td>
<td>88%</td>
</tr>
<tr>
<td><strong>AEs by severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 (mild)</td>
<td>28%</td>
<td>37%</td>
<td>53%</td>
<td>47%</td>
</tr>
<tr>
<td>Grade 2 (moderate)</td>
<td>54%</td>
<td>46%</td>
<td>30%</td>
<td>32%</td>
</tr>
<tr>
<td>Grade 3 (severe)</td>
<td>14%</td>
<td>16%</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>SAEs</td>
<td>3.5%</td>
<td>5.3%</td>
<td>3.5%</td>
<td>3.5%</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>-</td>
<td>-</td>
<td>0.9%</td>
<td>0.9%</td>
</tr>
</tbody>
</table>
## AEs in ≥ 10% of Patients with DMD

<table>
<thead>
<tr>
<th>AEs by Preferred Term</th>
<th>Study 007 Ataluren (N=57)</th>
<th>Study 007 Placebo (N=57)</th>
<th>Study 020 Ataluren (N=115)</th>
<th>Study 020 Placebo (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>56%</td>
<td>39%</td>
<td>23%</td>
<td>18%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>23%</td>
<td>23%</td>
<td>21%</td>
<td>19%</td>
</tr>
<tr>
<td>Fall</td>
<td>19%</td>
<td>12%</td>
<td>18%</td>
<td>17%</td>
</tr>
<tr>
<td>Headache</td>
<td>39%</td>
<td>25%</td>
<td>18%</td>
<td>18%</td>
</tr>
<tr>
<td>Cough</td>
<td>16%</td>
<td>19%</td>
<td>17%</td>
<td>11%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19%</td>
<td>25%</td>
<td>17%</td>
<td>9%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>25%</td>
<td>21%</td>
<td>14%</td>
<td>10%</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>12%</td>
<td>11%</td>
<td>9%</td>
<td>12%</td>
</tr>
</tbody>
</table>
Ataluren Well-Tolerated with Favorable Safety Profile in Patients with DMD

- Incidence of AEs similar between ataluren and placebo
  - Majority of AEs mild or moderate
  - Low incidence of SAEs
- No new ataluren risks identified from long-term treatment or post-marketing data
Summary of Benefit-Risk
A Clinical Perspective

Craig M. McDonald, MD
Director, Neuromuscular Disease Clinic
University of California, Davis Children’s Hospital
Study Chair, CINRG Duchenne Natural History Study
What Patients with DMD Need

- Effective, safe therapies which modify this devastating disease
- Modification of key milestones linked to quality and duration of life
- Maintain muscle function, including ambulation
- Preserve respiratory function
Loss of Ambulation Predicts for Subsequent Progression Milestones

Dx

5 Years

9 Years

NSAA Functions

Loss of Stair Climb

14 Years

Loss Ambulation

Loss of Upper Limb Function

20 Years

Ventilation

Death

Disease progression in DMD

Ataluren Preserves 6MWD, TFTs, NSAA and Predicts for Overall Delay in Disease Progression

Disease progression in DMD

Remarkably Consistent Evidence of Efficacy, Unlikely Due to Chance

- Key endpoints favor ataluren with 0.8% likelihood due to chance
  - 4 endpoints: 6MWT, 4-stair climb, 4-stair descend, 10m walk/run
  - 2 RCTs: Studies 007 and 020
- Loss of ambulation less in ataluren patients
- 15 of 17 NSAA measures for loss of function favor ataluren
- Pulmonary decline delayed in ataluren patients
Study 019 Extension Data Supports Preservation in Pulmonary Function by 4 Years with Ataluren

Absolute FVC Change = 13.8%* compared to matched CINRG patients

Breakpoints in slope with regard to age are indicated.
114 patients from the CINRG study matched to 54 patients from Study 019 based on age and steroid use.  
*p=0.005
Study 019: Age at Transition to FVC <1 L in Ataluren vs CINRG Non-Ambulatory Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th># FVC &lt;1 L</th>
<th>Median Age at FVC &lt;1 L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 019</td>
<td>38</td>
<td>3</td>
<td>Not reached</td>
</tr>
<tr>
<td>CINRG</td>
<td>58</td>
<td>23</td>
<td>18.8</td>
</tr>
</tbody>
</table>

Age (years)

Proportion with FVC ≥ 1L (%)

Log-rank p = 0.0317
CINRG study matched based on age and steroid use
Complete Loss of Function on NSAA, 1 to 0 Change, Different from 2 to 1 Change

Stand from Supine
NSAA: 1

Stand from Supine
NSAA: 0

Study 020 Placebo Arm Comparable to NSAA UK Population

*Courtesy of UK NorthStar Network analysis conducted by cTAP, 2016.*
Study 020: Ataluren Provides Preservation of NSAA Functions Over Time

Weeks

Cumulative post-baseline events

Ataluren

Placebo

(representative of NSAA UK)

Lin Wei Yang Ying (LWYY) approach, JRSS (B), 2000.

P=0.027
Today Marks an Opportunity to Advance Treatment for nmDMD

- Complex disease to treat and study, requiring scientific judgment
- Demonstrated production of dystrophin
  - Dystrophin production used for prior accelerated approval
- Sufficient evidence of efficacy from data presented
  - Slows disease progression
  - Delays functional loss milestones
- Minimal observed risks
Translarna™ (ataluren) for Duchenne Muscular Dystrophy

Peripheral and CNS Drug Advisory Committee (PCNSDAC)
Food and Drug Administration
September 28, 2017
Back-up Slides Shown
TFT Results Consistently in Favor of Ataluren (ITT)

**Study 007**
- **Ataluren (N=57)**: \(\Delta = 2.4\) s
- **Placebo (N=57)**: \(\Delta = 1.1\) s

**Study 020**
- **Ataluren (N=114)**: \(\Delta = 1.4\) s
- **Placebo (N=114)**: \(\Delta = 2.0\) s

**10m walk / run**
- **Ataluren**: \(1.0\) s
- **Placebo**: \(1.1\) s

**4-stair climb**
- **Ataluren**: \(2.0\) s
- **Placebo**: \(1.6\) s

**4-stair descend**
- **Ataluren**: \(2.0\) s
- **Placebo**: \(1.4\) s

Gray bar = 1.0 – 1.5 seconds

Study 007 ITT
- 10m walk / run \(p=0.316\), 4-stair climb \(p=0.041\), 4-stair descend \(p=0.197\)

Study 020 ITT
- 10m walk / run \(p=0.117\), 4-stair climb \(p=0.058\), 4-stair descend \(p=0.012\)
Study 019: Loss of Ambulation Analysis

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th># LOA</th>
<th>% LOA</th>
<th>Median Age at LOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataluren</td>
<td>49</td>
<td>24</td>
<td>49.0</td>
<td>16.3</td>
</tr>
</tbody>
</table>

Ambulatory Patients Age 9-18 at Study Entry
Age at Loss of Ambulation in Study 019 vs. CINRG

Study 019

All mutation subtypes

McDonald et al. Lancet 2017 (in press)  Corticosteroid treated
Recent Natural History Data Demonstrate Challenges of the 6MWT as an Endpoint in DMD for 12-Month Trials


**Data courtesy of H. Lee Sweeney, Ph.D. Myology Institute, University of Florida
Study 007: Demographic and Disease-Related Characteristics Were Balanced Between Arms in the >300 - ≤400m Subgroup

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment Arms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>N=22</td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>7.5 (2.22)</td>
</tr>
<tr>
<td>Body mass index, kg/m², mean (SD)</td>
<td>17.71 (3.54)</td>
</tr>
<tr>
<td>6MWD (m) at baseline, mean (SD)</td>
<td>342.34 (26.09)</td>
</tr>
<tr>
<td>Climb 4 stairs at baseline (sec), mean (SD)</td>
<td>5.13 (3.66)</td>
</tr>
<tr>
<td>Descend 4 stairs at baseline (sec), mean (SD)</td>
<td>4.67 (3.77)</td>
</tr>
<tr>
<td>Raise from supine at baseline (sec), mean (SD)</td>
<td>9.15 (9.22)</td>
</tr>
<tr>
<td>Run/Walk (sec), mean (SD)</td>
<td>6.54 (2.15)</td>
</tr>
<tr>
<td>Corticosteroid Use prior to randomization, n (%)</td>
<td></td>
</tr>
<tr>
<td>6 to &lt; 12 months</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>≥ 12 months</td>
<td>13 (59.1)</td>
</tr>
</tbody>
</table>
Postmarket RCT to Obtain Longer-Term Ataluren Efficacy and Safety

- 72-week placebo-controlled period followed with 72-week open-label extension
- Primary assessment on patients within Transition Phase
  - Secondary analyses will include all patients
- Expect results in 2021