# Pipeline Highlights 2016: Focus on Duchenne Muscular Dystrophy

Susan Trieu, Pharm.D.
Drug Information Pharmacist
MedImpact

AMCP Academy of Managed Care Pharmacy®

## Objectives

- *Discuss selected pipeline agents that will likely be of high impact/interest in 2016.*
- *Focus of discussion will be on pipeline agents for Duchenne Muscular Dystrophy.*
- *Discuss considerations for utilization management of these agents.*



AMCP Academy of Managed Care Pharmacy®

# PIPELINE HIGHLIGHTS 2016

AMCP Academy of Managed Care Pharmacy®

## Pipeline Agents- Cost Categories

| Cost Category | Description, Example |
|---|---|
| Displaced Cost | • New treatment regimen that will compete with current standard of care, for example:<br>  • Brand competition in previously generic market<br>  • Pipeline agent is same cost, more, or less expensive than current standard of care<br>  • Shift from medical cost to pharmacy cost |
| Additive Cost | • On top of current therapy (e.g., PCSK9 inhibitors + statins)<br>• Expands patient population treated (e.g., previously 10% now 50%) |
| New Cost | • Breakthrough Therapy - treatment in an area where no treatment previously existed |

www.amcp.org

AMCP Academy of Managed Care Pharmacy®

## *High Interest and Impact* Pipeline Agents *2016*

| Entity | Disease State | Anticipated FDA Decision | Route | Cost Category |
|---|---|---|---|---|
| reslizumab | Eosinophilic Asthma | March 29th, 2016 | IV | New Cost |
| Nuplazid (pimavanserin) | Parkinson's psychosis | May 1st, 2016 | Oral | New Cost |
| eteplirsen | Duchenne Muscular Dystrophy | May 26th, 2016 | IV | New Cost |

www.amcp.org

AMCP Academy of Managed Care Pharmacy



## *High Interest and Impact* Pipeline Agents *2016*

| Entity | Disease State | Anticipated FDA Decision | Route | Cost Category |
|---|---|---|---|---|
| obeticholic acid | Primary biliary cirrhosis | May 29th, 2016 | Oral | Additive Cost (PBC)<br>New Cost (NASH) |
| deutetrabenazine | Huntington's Disease | May 2016 | Oral | Displaced Cost |
| venetoclax | Chronic Lymphocytic Leukemia | June 2016 | Oral | Displaced Cost |

www.amcp.org

AMCP Academy of Managed Care Pharmacy

©2015 Academy of Managed Care Pharmacy

## *High Interest and Impact* Pipeline Agents *2016*

| Entity | Disease State | Anticipated FDA Decision | Route | Cost Category |
|---|---|---|---|---|
| velpatasvir/ sofosbuvir | Hepatitis C | June 28th, 2016 | Oral | New Cost |
| Translarna (ataluren) | Duchenne Muscular Dystrophy | 2nd-3rd Quarter 2016 | Oral | New Cost |
| andexanet alfa | Factor Xa Reversal | August 17th, 2016 | IV | New Cost |

www.amcp.org

AMCP Academy of Managed Care Pharmacy®



## *High Interest and Impact* Pipeline Agents *2016*

| Entity | Disease State | Anticipated FDA Decision | Route | Cost Category |
|---|---|---|---|---|
| Lixilan (insulin glargine/ lixisenatide) | Diabetes | August 2016 | SQ | Displaced Cost |
| Xultophy (insulin degludec/ liraglutide) | Diabetes | September 2016 | SQ | Displaced Cost |
| atezolizumab | Bladder Cancer | 3rd- 4th Quarter 2016 | IV | Additive Cost |
| Ocrevus (ocrelizumab) | Multiple Sclerosis | 4th Quarter 2016 | IV | Displaced Cost (RRMS) |
| | | | | New Cost (PPMS) |

www.amcp.org

AMCP Academy of Managed Care Pharmacy®

©2015 Academy of Managed Care Pharmacy

# DUCHENNE MUSCULAR DYSTROPHY (DMD)

## Muscular Dystrophy Overview

- Muscular dystrophy is a rare X-linked recessive disorder that results in progressive loss of muscle function
- Dystrophin is a protein encoded within the *DMD* gene that is essential for muscle cell function and integrity
- *DMD* gene contains 2.4 million base pairs and 79 exons
  - Mutations, mainly internal deletions, in the DMD gene result in abnormal or non-existent production of dystrophin
  - Lack of normal dystrophin causes muscle cell damage, muscle fiber loss, and replacement of functional muscle units by adipose and scar tissue

# Types of Muscular Dystrophy

**Duchenne Muscular Dystrophy (DMD)**

- Most common fatal genetic disorder diagnosed in early childhood
  - Symptoms begin in early childhood (usually before age 5) and progress to a loss of muscle function and loss of independence
- Affects approximately 1 in 3,500 males
- No functional dystrophin is produced

**Becker Muscular Dystrophy (BMD)**

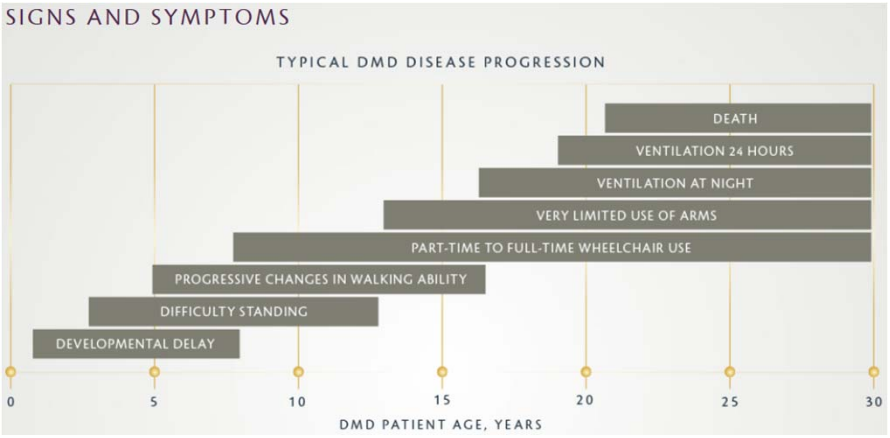
- Less severe form of muscular dystrophy
  - Symptoms begin during teenage years and progress to loss of function and varying degrees of loss of independence
- Affects approximately 1 in 20,000 males
- Abnormally functioning dystrophin is produced





# Diagnosis & Progression of DMD

- Suspicion of DMD upon family history or patient presentation
- Diagnosis is confirmed by genetic testing
- Muscle biopsy may be performed but is non-confirmatory

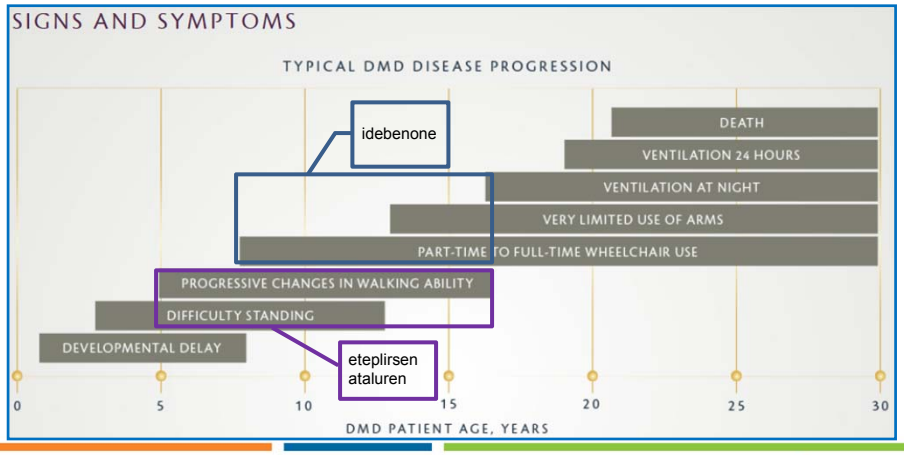





*http://www.sarepta.com/community/disease-resources*

# Diagnosis & Progression of DMD

- Suspicion of DMD upon family history or patient presentation
- Diagnosis is confirmed by genetic testing
- Muscle biopsy may be performed but is non-confirmatory




http://www.sarepta.com/community/disease-resources





# PIPELINE AGENTS: DMD

## Pipeline Agents: DMD

- Exon skipping agents
  - Kyndrisa (drisapersen) – did not get FDA approval
  - Exondys 51 (eteplirsen) – pending FDA approval
- Stop-codon read-through agents
  - Translarna (ataluren) – pending FDA approval
- Antioxidant and Mitochondrial Electron Transport agent
  - Raxone/Catena (idebenone)- preparation of filing with FDA

One of the key underlying issues facing the development of orphan drugs is their ability to demonstrate effectiveness when studying the prevalent portion of a rapidly progressing, heterogeneous, and/or exceedingly rare patient population



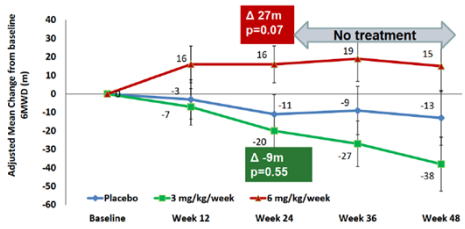


## EXON SKIPPING AGENTS

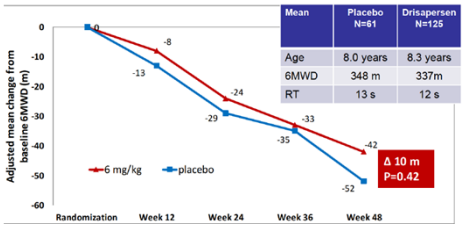
# Kyndrisa (drisapersen)

- **MOA**
  - Antisense oligonucleotide with a sequence specific to bind to exon 51 of dystrophin pre-mRNA causing the splicing machinery to skip over exon 51
- **Proposed Indication**
  - Treatment of DMD with mutations in the dystrophin gene that are amenable to exon 51 skipping as determined by genetic testing
- FDA issued complete response letter on January 14th 2016 stating that there was not substantial evidence of efficacy to support approval

Study 2




Study 3



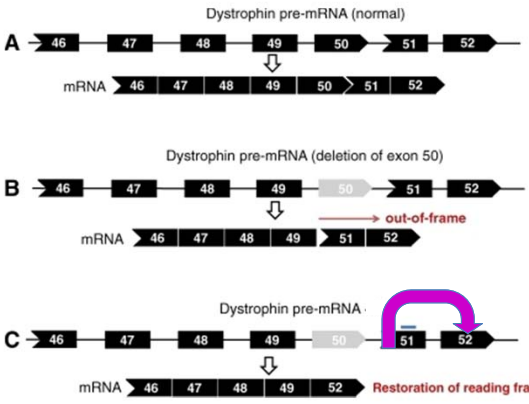

| Mean | Placebo N=61 | Drisapersen N=125 |
|---|---|---|
| Age | 8.0 years | 8.3 years |
| 6MWD | 348 m | 337m |
| RT | 13 s | 12 s |



*Kyndrisa FDA Briefing Document, 2015*



# Exon 51 Skipping – MOA




Production of fully functional protein

Production of protein is terminated

Production of truncated but partially functioning protein, similar to what is produced in BMD

# Exondys 51 (eteplirsen)

- FDA Advisory Committee meeting delayed
  - FDA decision date May 26th, 2016
- **MOA**
  - Phosphorodiamidate morpholino oligomer (PMO) that selectively binds to exon 51 of dystrophin pre-mRNA causing the splicing machinery to skip over exon 51, restoring the open reading frame
- **Proposed Indication**
  - Treatment of Duchenne muscular dystrophy (DMD) in patients who have confirmed mutation of the DMD gene that is amenable to exon 51 skipping
- **Target Population**
  - Approximately 13% (~2300) of DMD patients in the US have mutations amenable to exon 51 skipping but only ~1000 are ambulatory
- **Dose**
  - 30mg/kg/week intravenous infusion

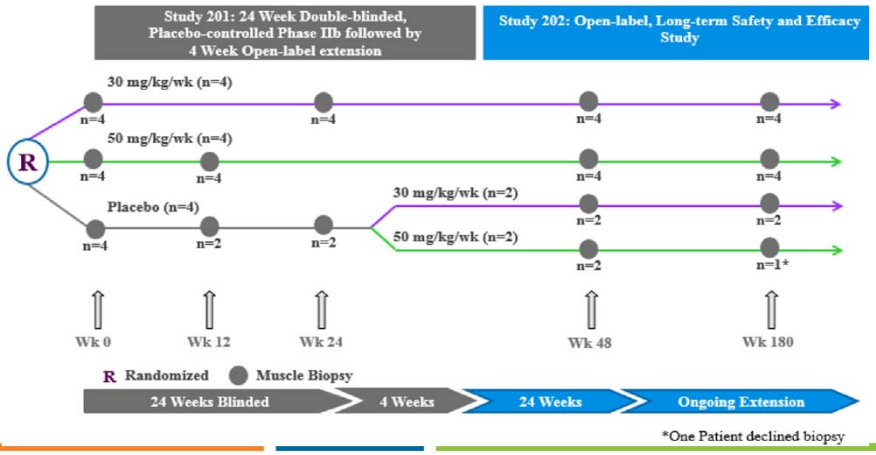




# Eteplirsen Phase IIb studies

Key Inclusion Criteria:
- Amenable to exon 51 skipping
- Between the ages of 7 and 13 years
- Baseline 6MWT between 200- 400 meters (±10%)
- Stable on oral corticosteroids for at least 24 weeks

Endpoints:
- Primary endpoint- change in dystrophin
- Secondary endpoint-6MWD

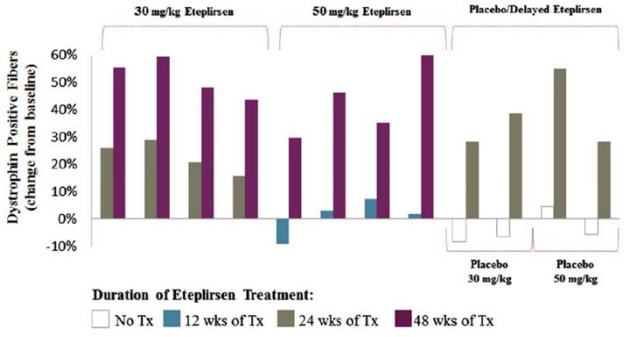



*One Patient declined biopsy



*Eteplirsen FDA Briefing Document, 2016*

# Eteplirsen – dystrophin production




*Mendell et al. 2013*

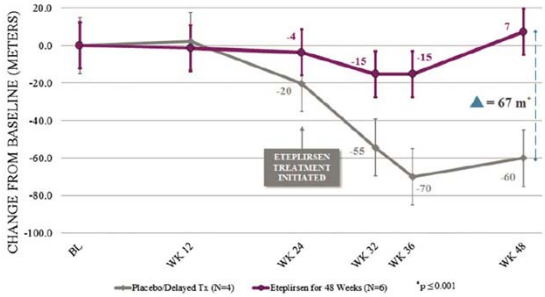
Increases in dystrophin seen at week 24 (30mg/kg group) and at week 48 (both eteplirsen doses)

- Reliability of results questionable
  - *"FDA conducted an inspection of the facility where the [dystrophin] images had been analyzed, and some methodological concerns were identified."*

# Eteplirsen – 6MWD

| | Placebo | 30mg/kg | 50mg/kg |
|---|---|---|---|
| Week 24 | -25.8m | -128.2m | -0.3m |
| Adjusted* | | +14.4m | |
| Week 48 | -68.4m | -153.4m | +21m |
| Adjusted* | | +31.5m | |

*Analysis excluded 2 patients in the 30mg/kg group who lost ambulation shortly after enrollment




www.amcp.org

*Mendell et al. 2013*

AMCP Academy of Managed Care Pharmacy

# Eteplirsen – Safety

- No significant treatment-related adverse effects through 168 weeks
  - No hospitalizations, treatment discontinuations, or interruptions

| Common Adverse Events After 24 Weeks (Study 201) | | | |
|---|---|---|---|
| | Placebo (n = 4) | Etep 30mg/kg (n = 4) | Etep 50mg/kg (n = 4) |
| Procedural pain | 3 (75%) | 1 (25%) | 3 (75%) |
| Oropharyngeal pain | 3 (75%) | 3 (75%) | 0 |
| Hypokalemia | 2 (50%) | 2 (50%) | 2 (50%) |
| Pyrexia | 2 (50%) | 1 (25%) | 0 |
| Vomiting | 0 | 1 (25%) | 2 (50%) |
| Contact dermatitis | 0 | 2 (50%) | 0 |

- Lack of adverse events may be due to eteplirsen being non-charged molecule





## STOP CODON READ-THROUGH AGENTS

AMCP Academy of Managed Care Pharmacy®

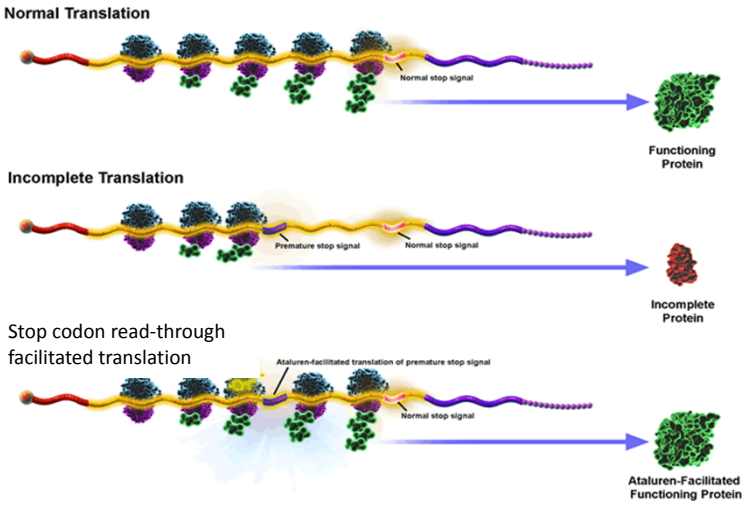
# Translarna (ataluren)

FDA rolling submission completed January 8th
- Orphan disease & fast-track designation

- **MOA**
  - Enables read-through of a premature stop codon associated with a nonsense mutation
- **Proposed Indications**
  - Treatment of nmDMD in ambulatory patients
- **Target Population**
  - Separate 13% (~2300) of DMD patients in the US have DMD due to non-sense mutations but only ~1000 are ambulatory
- **Dose**
  - *Likely to be* 10mg-10mg-20mg/kg/day (40mg/kg/day) oral granules for suspension



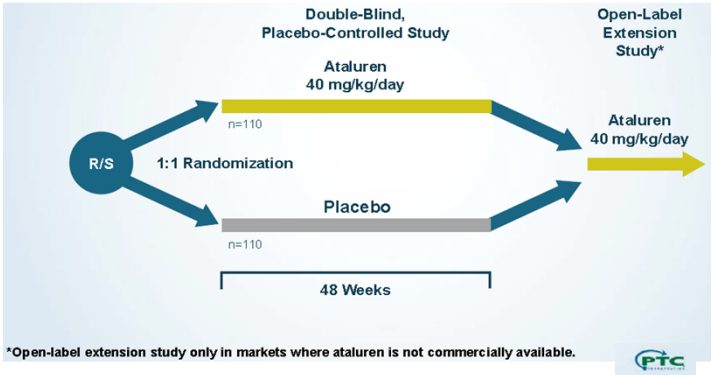

# Stop Codon Read-Through - MOA






*Adapted from Haas et al. 2015*

# Ataluren ACT DMD Phase III




**Primary outcome measure:**
- 6MWD (change from baseline)

**Secondary outcome measure:**
- Timed-function tests
- North Star
- PODCI QoL

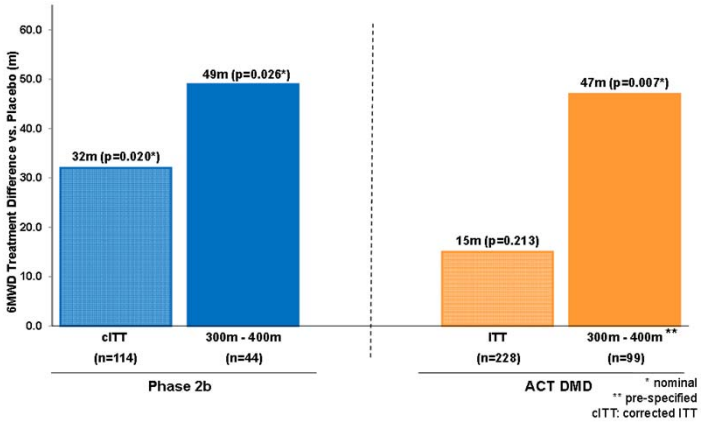
| Eligibility Criteria | Stratification |
|---|---|
| ≥7 years & ≤16 years<br>Steroid use<br>6MWD ≥150 m<br>≤80% of predicted for age and height | ≥350 m vs <350 m<br>≥9 years vs <9 years |





# Ataluren 6MWD phase IIb vs phase III

- Change at 48 weeks from baseline in overall populations and subgroups






*ACT DMD Clinical Trial Supplementary Information, 2015*

# Ataluren – Safety

**Phase IIb study**

- No study discontinuations due to adverse events
- Most common adverse events in Translarna 40mg/kg/d vs 80mg/kg/d vs placebo-treated patients were:
  - Vomiting (56.1% vs 45.0% vs 38.6%)
  - Headache (38.6% vs 25.0% vs 24.6%)
  - Diarrhea (19.3% vs 28.3% vs 24.6%)
  - Nasopharyngitis (22.8% vs 16.7% vs 22.8%)
  - Pyrexia (24.6% vs 11.7% vs 21.1%)
  - Cough (15.8% vs 21.7% vs 19.3%)

**ACT DMD**

- One patient in each study arm discontinued treatment due to adverse event
- Most common adverse events in Translarna- vs placebo-treated patients were:
  - Vomiting (22.6% vs 18.3%)
  - Nasopharyngitis (20.9% vs 19.1%)
  - Fall (19.1% vs 17.4%)
  - Cough (16.5% vs 11.3%)
  - Headache (18.3% for both groups)





## ANTIOXIDANT/ MITOCHONDRIAL ELECTRON TRANSPORT AGENT

AMCP Academy of Managed Care Pharmacy®

# Raxone/Catena (idebenone)

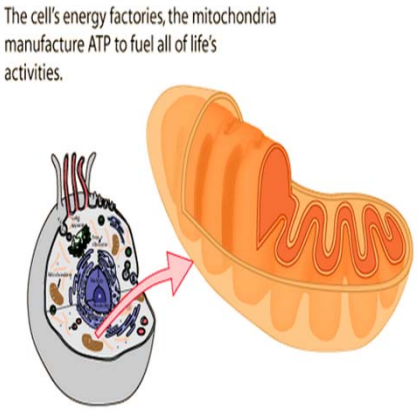
- Preparing for FDA filing, anticipated for 1st or 2nd Quarter of 2016
- **MOA**
  - Synthetic short-chain benzoquinone and a substrate for the enzyme NAD(P)H: quinone oxidoreductase (NQO1) capable of stimulating mitochondrial electron transport, supplementing cellular energy levels and inhibiting reactive oxygen species (ROS) production
- **Proposed Indication (*speculated*)**
  - Treatment of Duchenne muscular dystrophy (DMD) in patients 8 years and older who are intolerant of oral corticosteroids.
- **Target Population**
  - US DMD population ~ 12,800 patients
  - Target population ~ 5120 patients in US (accounts for age and steroid non-users)
- **Dose**
  - 900mg/day (2 tablets TID)




# Idebenone- MOA

**Mitochondrial Dysfunction**

- Dystrophin causes $Ca^{2+}$ influx which causes mitochondrial dysfunction
- Mitochondrial dysfunction leads to increases in ROS
- Idebenone
  - Stimulates mitochondrial electron transfer chain
    - Reduces formation of ROS
    - Increases cellular energy (ATP)



# Idebenone Phase III Trial- DELOS

Patient Characteristics:
- Age 10-18 years old (mean age: 14.3 years old)
- No selection for mutational status
- Patients off chronic steroids
- > 90% of patients non-ambulatory
- Baseline PEF%p ≤ 80

Idebenone 900mg/day
N=31

Placebo
N= 33

52 Weeks

**Primary Endpoint:** Change in spirometer-measured peak expiratory flow as percentage predicted (PEF%p) from baseline to 52 weeks.

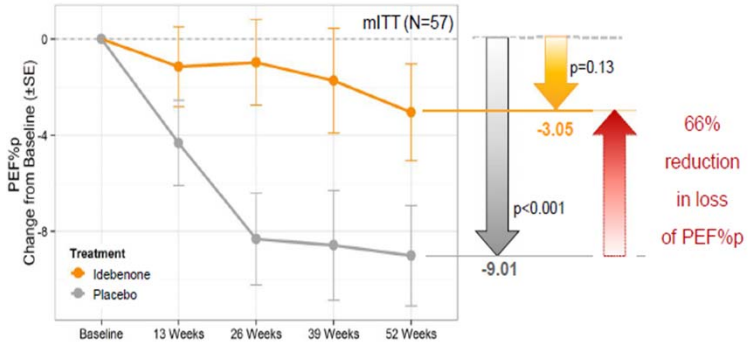


Buyse et al: Lancet 2015; 385: 1748-57.



# Primary Endpoint: change in PEF%p (mITT)

(hospital-based spirometry)




| | | | | | | |
|---|---|---|---|---|---|---|
| Difference | 3.17 | 7.35 | 6.84 | 5.96 | Average Difference | 5.83 |
| **p-value** | **0.20** | **0.01** | **0.03** | **0.04** | **p-value** | **0.02** |



http://www.santhera.com/downloads/15-04-24_Buyse_AAN.pdf

# Idebenone Safety- DELOS Trial

- 66 patients were included in safety analysis
- Some of the more common adverse events are seen below
- 4 total patients discontinued treatment (2 in each arm) but it was not judged to be related to study treatment

| | Idebenone (n= 32) | Placebo (n=34) |
|---|---|---|
| Any Adverse Event | 94% | 94% |
| Nasopharyngitis | 26% | 26% |
| Headache | 20% | 20% |
| Diarrhea | 25% | 12% |



Buyse et al: Lancet 2015; 385: 1748-57.



# CONSIDERATIONS FOR UTILIZATION MANAGEMENT

## Coverage Considerations

- Overall Value Proposition
  - How does payer determine value?
- Appropriate Use
  - FDA label
  - Clinical trial population
- When do you stop therapy?
- Combination Therapy?
- Indication Expansion




## Utilization Management Considerations

| | |
|---|---|
| drisapersen<br>eteplirsen | • Patient population<br>• Confirmed genetic test, age, ambulation<br>• Duration, renewal criteria<br>• Prescriber restriction – DMD Tx Center<br>• Steroid Use |
| ataluren | • Patient population<br>• Confirmed genetic test, age, ambulation<br>• Duration |
| idebenone | • Patient population<br>• Diagnosis, age, ambulation, steroid use<br>• Duration |

# Thank you

- *Special thank you to colleague Jora Sliwinski, PharmD*