Pipeline Highlights 2016: Focus on Duchenne Muscular Dystrophy

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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.
# PIPELINE HIGHLIGHTS 2016

## Pipeline Agents - Cost Categories

<table>
<thead>
<tr>
<th>Cost Category</th>
<th>Description, Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Displaced Cost</td>
<td>• New treatment regimen that will compete with current standard of care, for example:</td>
</tr>
<tr>
<td></td>
<td>• Brand competition in previously generic market</td>
</tr>
<tr>
<td></td>
<td>• Pipeline agent is same cost, more, or less expensive than current standard of care</td>
</tr>
<tr>
<td></td>
<td>• Shift from medical cost to pharmacy cost</td>
</tr>
<tr>
<td>Additive Cost</td>
<td>• On top of current therapy (e.g., PCSK9 inhibitors + statins)</td>
</tr>
<tr>
<td></td>
<td>• Expands patient population treated (e.g., previously 10% now 50%)</td>
</tr>
<tr>
<td>New Cost</td>
<td>• Breakthrough Therapy - treatment in an area where no treatment previously existed</td>
</tr>
</tbody>
</table>
### High Interest and Impact Pipeline Agents 2016

<table>
<thead>
<tr>
<th>Entity</th>
<th>Disease State</th>
<th>Anticipated FDA Decision</th>
<th>Route</th>
<th>Cost Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>reslizumab</td>
<td>Eosinophilic Asthma</td>
<td>March 29th, 2016</td>
<td>IV</td>
<td>New Cost</td>
</tr>
<tr>
<td>Nuplazid (pimavanserin)</td>
<td>Parkinson’s psychosis</td>
<td>May 1st, 2016</td>
<td>Oral</td>
<td>New Cost</td>
</tr>
<tr>
<td>eteplirsen</td>
<td>Duchenne Muscular Dystrophy</td>
<td>May 26th, 2016</td>
<td>IV</td>
<td>New Cost</td>
</tr>
<tr>
<td>obeticholic acid</td>
<td>Primary biliary cirrhosis</td>
<td>May 29th, 2016</td>
<td>Oral</td>
<td>Additive Cost (PBC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>New Cost (NASH)</td>
</tr>
<tr>
<td>deutetrabenazine</td>
<td>Huntington’s Disease</td>
<td>May 2016</td>
<td>Oral</td>
<td>Displaced Cost</td>
</tr>
<tr>
<td>venetoclax</td>
<td>Chronic Lymphocytic Leukemia</td>
<td>June 2016</td>
<td>Oral</td>
<td>Displaced Cost</td>
</tr>
<tr>
<td>Entity</td>
<td>Disease State</td>
<td>Anticipated FDA Decision</td>
<td>Route</td>
<td>Cost Category</td>
</tr>
<tr>
<td>-----------------</td>
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<td>---------------</td>
</tr>
<tr>
<td>velpatasvir/sofosbuvir</td>
<td>Hepatitis C</td>
<td>June 28th, 2016</td>
<td>Oral</td>
<td>New Cost</td>
</tr>
<tr>
<td>Translarna (ataluren)</td>
<td>Duchenne Muscular Dystrophy</td>
<td>2nd-3rd Quarter 2016</td>
<td>Oral</td>
<td>New Cost</td>
</tr>
<tr>
<td>andexanet alfa</td>
<td>Factor Xa Reversal</td>
<td>August 17th, 2016</td>
<td>IV</td>
<td>New Cost</td>
</tr>
</tbody>
</table>

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

![Typical DMD Disease Progression Graph](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.
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

www.amcp.org

**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

www.amcp.org
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
Eteplirsen – dystrophin production

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

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

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Eteplirsen – 6MWD

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>30mg/kg</th>
<th>50mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 24</td>
<td>-25.8m</td>
<td>-128.2m</td>
<td>-0.3m</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>+14.4m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 48</td>
<td>-68.4m</td>
<td>-153.4m</td>
<td>+21m</td>
</tr>
<tr>
<td>Adjusted*</td>
<td></td>
<td>+31.5m</td>
<td></td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Common Adverse Events After 24 Weeks (Study 201)</th>
<th>Placebo (n = 4)</th>
<th>Etep 30mg/kg (n = 4)</th>
<th>Etep 50mg/kg (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedural pain</td>
<td>3 (75%)</td>
<td>1 (25%)</td>
<td>3 (75%)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>3 (75%)</td>
<td>3 (75%)</td>
<td>0</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>2 (50%)</td>
<td>2 (50%)</td>
<td>2 (50%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2 (50%)</td>
<td>1 (25%)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>1 (25%)</td>
<td>2 (50%)</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>0</td>
<td>2 (50%)</td>
<td>0</td>
</tr>
</tbody>
</table>

- Lack of adverse events may be due to eteplirsen being non-charged molecule
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 nonsense mutations but only ~1000 are ambulatory

- **Dose**
  - *Likely to be* 10mg-10mg-20mg/kg/day (40mg/kg/day) oral granules for suspension

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Stop Codon Read-Through - MOA

- **Normal Translation**
  - Protein synthesis continues normally

- **Incomplete Translation**
  - Translation is incomplete due to premature stop codon

- **Stop codon read-through facilitated translation**
  - Ataluren enables reading through of the premature stop codon

Adapted from Haas et al. 2015
Ataluren ACT DMD Phase III

Double-Blind, Placebo-Controlled Study

- Ataluren 40 mg/kg/day, n=110
- Placebo, n=110

1:1 Randomization

48 Weeks

Open-Label Extension Study

- Ataluren 40 mg/kg/day

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

Secondary outcome measure:
- Timed-function tests
- North Star
- POQI QoL

Eligibility Criteria
- 27 years ≤ 16 years
- Steroid use
- 6MWD ≥ 150 m
- ≥80% of predicted for age and height

Stratification
- ≥350 m vs <350 m
- ≥9 years vs <9 years

Ataluren 6MWD phase IIb vs phase III

• Change at 48 weeks from baseline in overall populations and subgroups
### 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)

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**ANTIOXIDANT/ MITOCHONDRIAL ELECTRON TRANSPORT AGENT**
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)

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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

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

Primary Endpoint: change in PEF%p (mITT)
(hospital-based spirometry)

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

<table>
<thead>
<tr>
<th></th>
<th>Idebenone (n=32)</th>
<th>Placebo (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Event</td>
<td>94%</td>
<td>94%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>26%</td>
<td>26%</td>
</tr>
<tr>
<td>Headache</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25%</td>
<td>12%</td>
</tr>
</tbody>
</table>

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

- **dritisensen**
  - Patient population
  - Confirmed genetic test, age, ambulation
  - Duration, renewal criteria
  - Prescriber restriction – DMD Tx Center
  - Steroid Use

- **eteplirsen**
  - Patient population
  - Confirmed genetic test, age, ambulation
  - Diagnosis, age, ambulation, steroid use
  - Duration

- **ataluren**
  - Patient population
  - Confirmed genetic test, age, ambulation
  - Duration

- **idebenone**
  - Patient population
  - Diagnosis, age, ambulation, steroid use
  - Duration
Thank you

- Special thank you to colleague Jora Sliwinski, PharmD