Gene Therapy & Neurodegenerative Disorders

Clinical Pipeline & Sector Overview

Janet Lambert, CEO
November 15, 2018
About ARM

- **International advocacy organization**
  - Dedicated to realizing the promise of safe and effective regenerative medicines for patients around the world

- **300+ Members**
  - Small and large companies, non-profit research institutions, patient organizations, and other sector stakeholders

- **Priorities:**
  - Clear, predictable, and harmonized regulatory pathways
  - Enabling market access and value-based reimbursement policies
  - Addressing industrialization and manufacturing hurdles
  - Conducting key stakeholder outreach, communication, and education
  - Facilitating sustainable access to capital
Gene Therapy Clinical Pipeline: Sector Overview

- **Global Sector Overview:** 2018
- **Clinical Progress:** YTD 2018
- **Anticipated Clinical Data Events:** 2018+
- **Sector Financings:** YTD 2018
- **Policy Environment:** 2018 and beyond
A Quick Note -

This presentation will be available via:

• **ARM’s website:** www.alliancerm.org
• **Twitter:** @alliancerm
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Regenerative Medicine Companies Worldwide, including Gene and Cell Therapies, and Tissue Engineering Therapeutic Developers

Current Global Sector Landscape

476 North America

235 Europe & Israel

142 Asia

23 Oceania
Australia, New Zealand, Marshall Islands

1 Africa

15 South America

Source data provided by: informa
Current Global Sector Landscape

382 Gene Therapy & Gene-Based Medicine Companies Worldwide

Europe & Israel: 101
Asia: 70
Oceania: 7
North America: 206
South America: 2

Source data provided by: informa
Gene Therapy & Gene-Based Medicine Companies Active in Neurodegenerative Indications

Current Global Sector Landscape

Source data provided by: informa
Significant Therapeutic Developers in Gene Therapy for Neurodegenerative Disorders

**Clinical stage:**
- Amicus Therapeutics
- Axovant (licensed from Oxford Biomedica)
- bluebird bio
- GenSight Biologics
- Orchard Therapeutics (acquired from GSK)
- Oxford Biomedica
- REGENXBIO
- Takara / Gene Therapy Research Institution
- uniQure NV
- Viromed
- Voyager Therapeutics

**Pre-clinical:**
- Abbvie (partnered with Voyager)
- Abeona Therapeutics
- Adverum Therapeutics (through Annapurna acquisition)
- AskBio
- Avexis / Novartis (through REGENXBIO partnership)
- BrainVectas
- Elixirgen
- Homology Medicines
- MeiraGTx
- Novartis (collaboration with REGENXBIO)
- Pfizer (through Bamboo acquisition)
- Prevail Therapeutics
- PTC Therapeutics (through Agilis acquisition)
- Sangamo Therapeutics
- Sanofi Genzyme (through Voyager partnership)
- Spark Therapeutics
- Vybion
- Xalud Therapeutics
• **Viral vectors:** retroviruses, adenoviruses, herpes simplex, vaccinia, and adeno-associated virus (AAV)

• **Non-viral vectors:** nanoparticles and nanospheres

• **Genetically modified cell-based immunotherapies:** chimeric antigen receptors (CAR) T cell therapies, T cell receptor (TCR) therapies, natural killer (NK) cell therapies, tumor infiltrating lymphocytes (TILs), marrow derived lymphocytes (MILs), gammadelta T cells, and dendritic vaccines.

• **Gene editing:** meganucleases, homing endonucleases; zinc finger nucleases (ZFNs); transcription activator-like effector-based nucleases (TALEN); nucleases such as Cas9 and Cas12a that derive from the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR/Cas); homologous recombination of adeno-associated virus (AAV)-derived sequences.
Gene Therapy Focus: Neurodegenerative Disorders

- Alzheimer's disease (AD) and other taupathies/dementias
- Huntington's disease (HD)
- Parkinson's disease (PD)
- Amyotrophic Lateral Sclerosis (ALS) and other Motor Neuron diseases
- Ataxias (including spinocerebellar ataxia and Friedreich's ataxia)
- Multiple sclerosis (MS)
- Adrenoleukodystrophy and Metachromatic Leukodystrophy
- Neuropathies
- Batten disease (BD)
Gene & Gene-Modified Cell Therapy Clinical Trials by Phase

**Phase I**
- Total: 259
- Gene Therapy: 114
- Gene-Modified Cell Therapy: 145

**Phase II**
- Total: 372
- Gene Therapy: 204
- Gene-Modified Cell Therapy: 168

**Phase III**
- Total: 48
- Gene Therapy: 33
- Gene-Modified Cell Therapy: 15

Source data provided by: informa
Gene Therapy Clinical Trials for Neurodegenerative Indications

By Indication

- Parkinson's disease, 6
- Alzheimer's disease, 1
- Diabetic Neuropathy, 1
- Charcot-Marie-Tooth Neuropathy, 1
- Giant Axonal Neuropathy, 1
- Amyotrophic Lateral Sclerosis, 1
- Lysosomal Storage Diseases, 6
- Leber Hereditary Optic Neuropathy, 6
- Batten Disease, 2

By Phase

- Phase I, 6
- Phase I/II, 11
- Phase II, 1
- Phase II/III, 2
- Phase III, 5

Source data provided by: informa
Approved Gene Therapy & Gene-Modified Cell Therapy Products

Recent approvals:

• Spark Therapeutics’ **LUXTURNA** gene therapy for biallelic RPE65-mediated inherited retinal disease
  • received positive CHMP opinion – September 21, 2018
  • Approved by the FDA – December 19, 2017

• Gilead / Kite Pharma’s **Yescarta** CAR-T therapy
  • received approval from the EC for the treatment of DLBCL – August 27
  • Received approval from the EC to treat adult patients with r/r DLBCL and PMBCL – August 27

• Novartis’s **Kymriah** CAR-T therapy
  • received FDA approval for a second indication: treatment of adult patients with r/r large B-cell lymphoma – May 1
  • Approved by the EC for adult patients with r/r DLBCL and patients under the age of 25 with ALL – August 27
### Select Anticipated Clinical Data & Events in Neurodegenerative Disease: 2018+

<table>
<thead>
<tr>
<th>Company</th>
<th>Product</th>
<th>Technology</th>
<th>Indication</th>
<th>Clinical Stage</th>
<th>Expected Reporting Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orchard Therapeutics</td>
<td>OTL-200</td>
<td>Gene therapy</td>
<td>Metachromatic leukodystrophy</td>
<td>MAA filing, BLA submission</td>
<td>Anticipates filing BLA, MAA in 2020</td>
</tr>
<tr>
<td>bluebird bio</td>
<td>Lenti-D</td>
<td>Gene therapy</td>
<td>Cerebral Adrenoleukodystrophy</td>
<td>Ph III</td>
<td>Ph III study to be initiated in 2019</td>
</tr>
<tr>
<td>Brainstorm Tx</td>
<td>NurOwn</td>
<td>Mesenchymal Stem Cell Therapy</td>
<td>ALS</td>
<td>Ph III</td>
<td>Enrollment to be completed by mid-2019</td>
</tr>
<tr>
<td>Axovant</td>
<td>AXO-Lenti-PD</td>
<td>Gene therapy</td>
<td>Parkinson’s disease</td>
<td>Ph I/II</td>
<td>Initial data from Cohort 1 expected 1H 2019</td>
</tr>
<tr>
<td>Kadimastem</td>
<td>AstroRx</td>
<td>Astrocyte cell therapy</td>
<td>ALS</td>
<td>Ph I/IIa</td>
<td>Initial data from Cohort A expected mid-2019</td>
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<tr>
<td>BlueRock Therapeutics</td>
<td>Undisclosed</td>
<td>iPSC cell therapy</td>
<td>Parkinson’s disease</td>
<td>IND submission</td>
<td>IND to be submitted in 2018; first patient treated EOY 2018</td>
</tr>
<tr>
<td>uniQure</td>
<td>AMT-130</td>
<td>AAV Gene Therapy</td>
<td>Huntington’s disease</td>
<td>IND submission</td>
<td>IND submission in EOY 2018; begin dosing 2019</td>
</tr>
<tr>
<td>AveXis</td>
<td>AVXS-201</td>
<td>Gene therapy</td>
<td>Genetic ALS (SOD1)</td>
<td>Pre-IND</td>
<td>IND submission expected in late 2018/early 2019</td>
</tr>
<tr>
<td>PTC Therapeutics</td>
<td>Undisclosed</td>
<td>Gene therapy</td>
<td>Friedreich ataxia</td>
<td>pre-IND</td>
<td>Expected to submit IND in 2019</td>
</tr>
</tbody>
</table>

Full list available on ARM’s website: [https://alliancerm.org/anticipated-data-events/](https://alliancerm.org/anticipated-data-events/)

Source: Company-provided or publicly-available information
Global Financings

$2.8B
Q3 2018
Total Global Financings
(all technologies)

$10.7B
YTD 2018
Total Global Financings
(all technologies)

$2.1B
Q3 2018
Total Gene-Based Therapies Financings

$7.8B
YTD 2018
Total Gene-Based Therapies Financings

59% increase from Q3 2017 YoY

40% increase YoY

35% increase from Q3 2017 YoY

34% increase YoY
**FDA’s RMAT Designation**

**Product sponsor benefits:**
- Guaranteed interactions with the FDA.
- Eligibility for priority review and accelerated approval.
- Flexibility in the number of clinical sites used and the possibility to use patient registry data and other sources of “real-world” evidence for post-approval studies (pending FDA approval).

**Implementation:**
- ARM advocated that gene therapies qualify; FDA confirmed late 2017.
- 28 products have received the designation (as of Nov. 2018) – 24 have announced publicly

**8 gene therapies have RMAT designation:**
1. Abeona EB-101 (recessive dystrophic EB)
2. Abeona ABO-102 AAV gene therapy (MPS IIIA)
3. Audentes Tx’s AT132 (X-Linked Myotubular Myopathy)
4. bluebird bio’s LentiGlobin (severe sickle cell disease)
5. Juno / Celgene JCAR017 CAR-T (r/r diffuse large B-cell lymphoma)
6. Nightstar Tx’s NSR-REP1 (choroideremia)
7. Poseida Tx P-BCMA-101 CAR-T (multiple myeloma)
8. Voyager Tx’s VY-AADC (Parkinson’s Disease)
Supportive Policy Environment – United States

• FDA:
  • RMAT designation
  • FDA’s 6 new draft guidances for gene therapy
    • Draft Guidance on Human Gene Therapy for Rare Disease:
      • Discusses considerations for trial sponsors, including statistical considerations of small study population size, the use of single-arm trial designs, and the use of patient experience data
  • Sector supportive U.S. FDA Commissioner Scott Gottlieb:

  “We’re at a key point when it comes to cell and gene therapy. These therapies have the potential to address hundreds, if not thousands, of different rare and common diseases [...] The field is moving ahead rapidly, and our FDA scientists are focused on addressing the challenges in manufacturing and clinical development that arise.”

  - Remarks from Commissioner Gottlieb at ARM’s RMAT policy lunch, May 2018
Key Takeaways

**Supportive policy environment:**
- U.S., EU, and globally

**Strong scientific data:**
- Potential for positive, widespread patient impact
- Increase in the number of clinical trials in CNS and overall

**Sustained investor, partnering interest:**
- Substantial year-over-year increases in investment and financings overall and in gene-based therapies

**Commercial opportunities and challenges:**
- Transformative gene therapy products for certain indications already on the market; many more to come near-term
- Success dependent on addressing market access, regulatory convergence, and industrialization issues
Thank You!