Gene Therapy & Neurodegenerative Disorders

Clinical Pipeline & Sector Overview

Janet Lambert, CEO

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Alliance *for* Regenerative Medicine

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**

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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

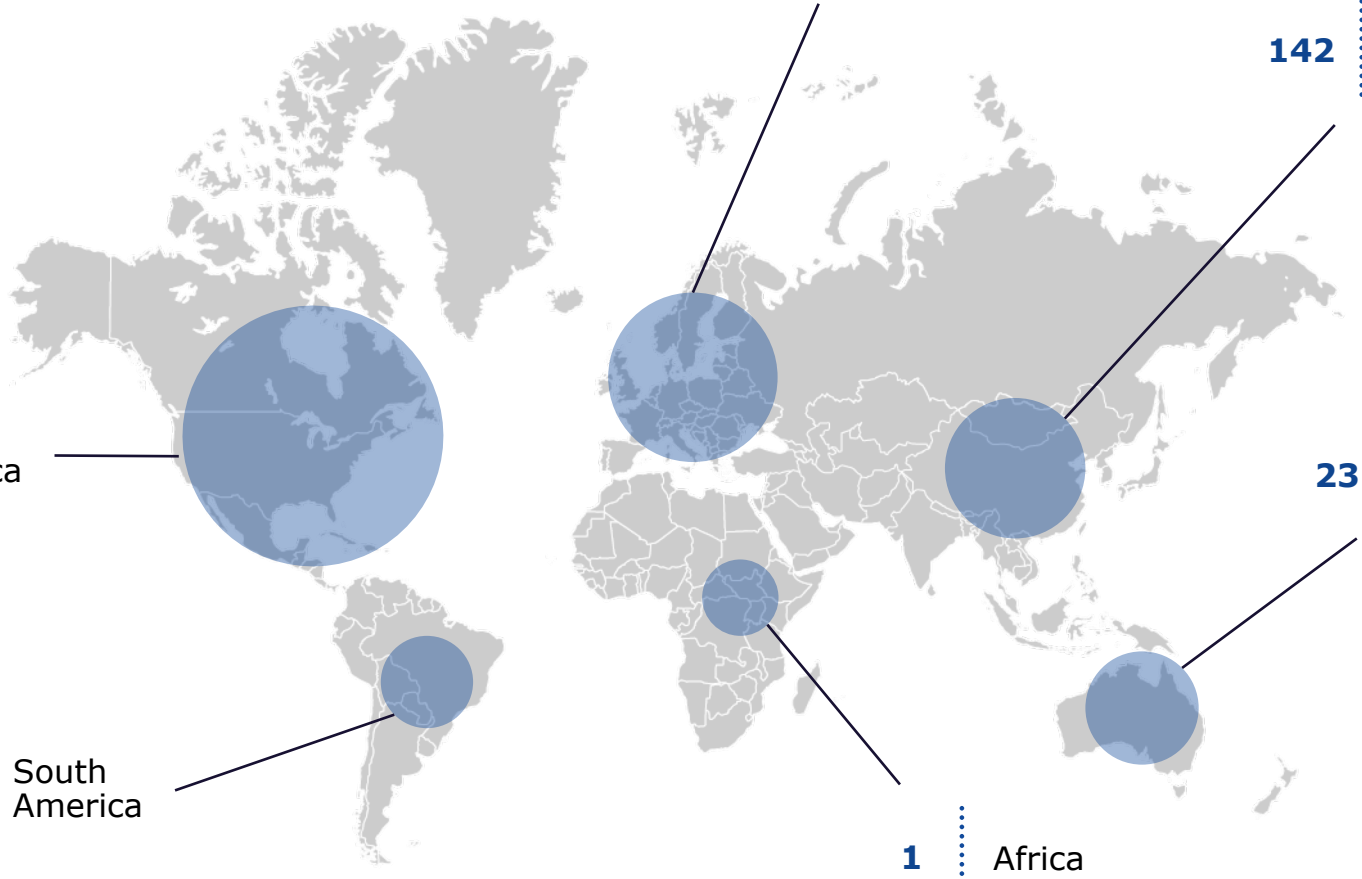
A Quick Note -

This presentation will be available via:

- **ARM's website: www.alliancerm.org**
- **Twitter @alliancerm**

Current Global Sector Landscape

892
Regenerative Medicine Companies Worldwide, including Gene and Cell Therapies, and Tissue Engineering Therapeutic Developers



235 Europe & Israel

142 Asia

476 North America

23 Oceania
Australia, New Zealand, Marshall Islands

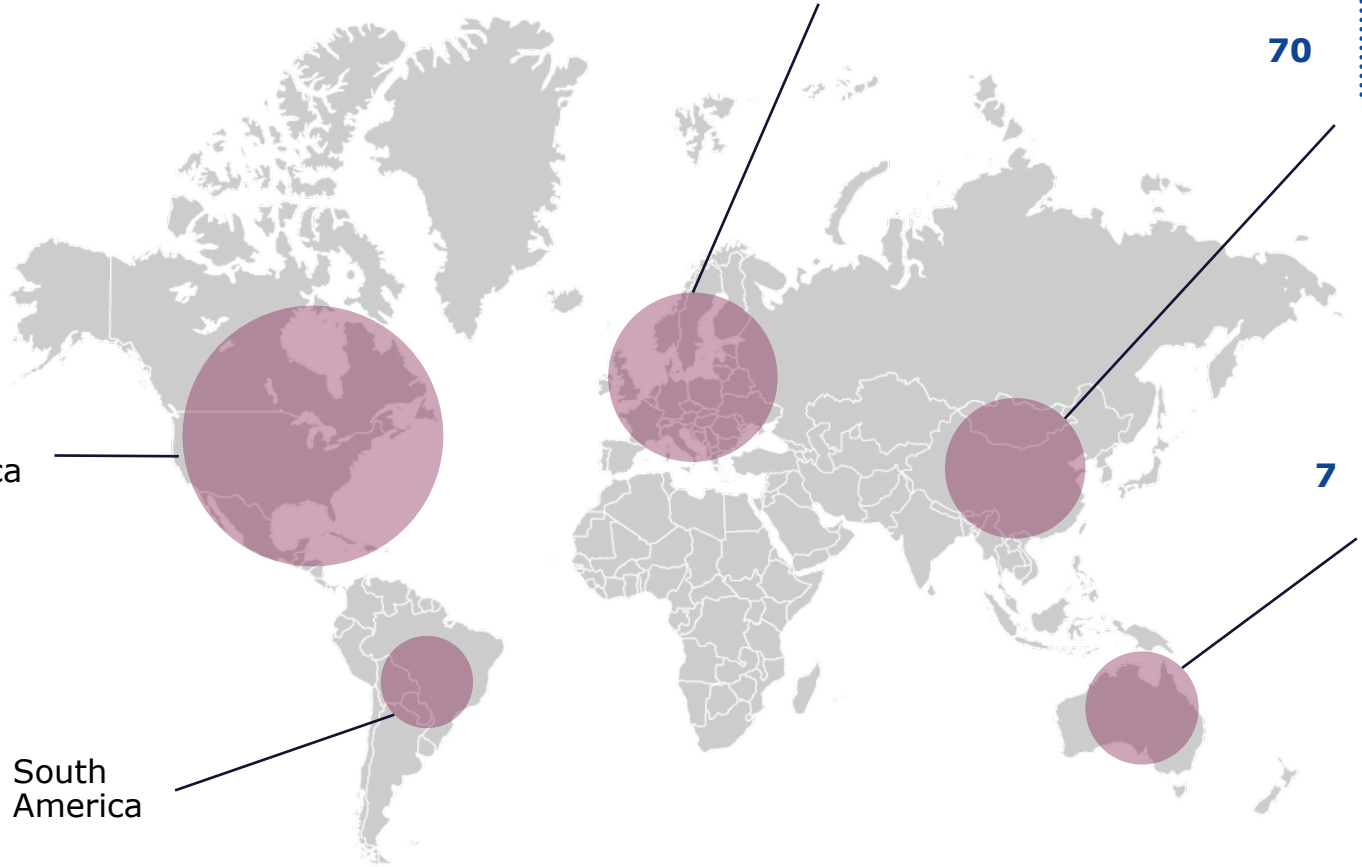
15 South America

1 Africa

Source data provided by: informa

Current Global Sector Landscape

382
Gene Therapy & Gene-Based Medicine Companies Worldwide



101 Europe & Israel

70 Asia

206 North America

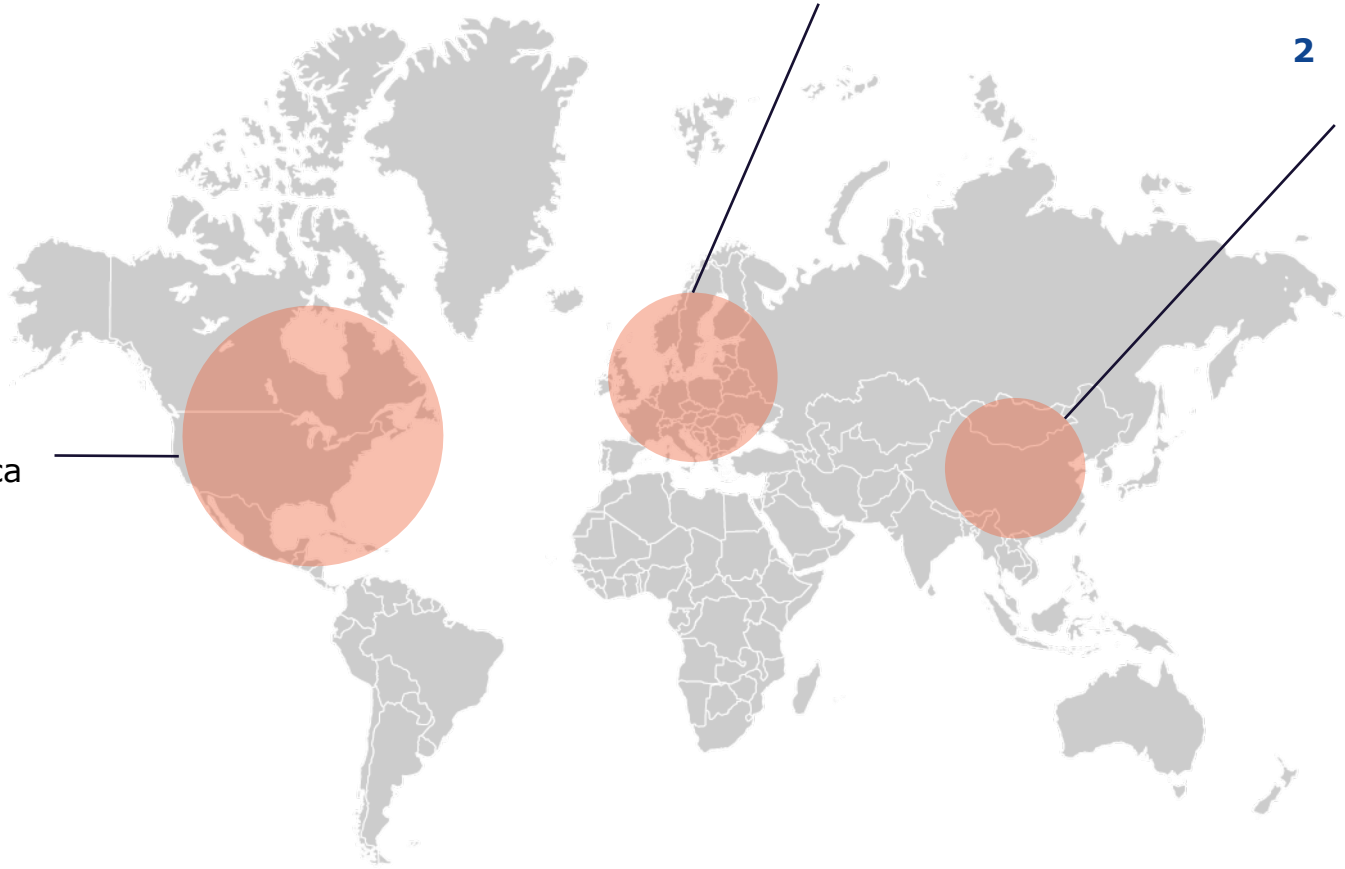
7 Oceania
Australia, New Zealand, Marshall Islands

2 South America

Source data provided by: informa

Current Global Sector Landscape

29
Gene Therapy & Gene-Based Medicine Companies Active in Neurodegenerative Indications



Source data provided by: informa

Significant Therapeutic Developers in Gene Therapy for Neurodegenerative Disorders

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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

Major Gene-Based Therapeutic Platforms & Enabling Technologies

- **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

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- 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

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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

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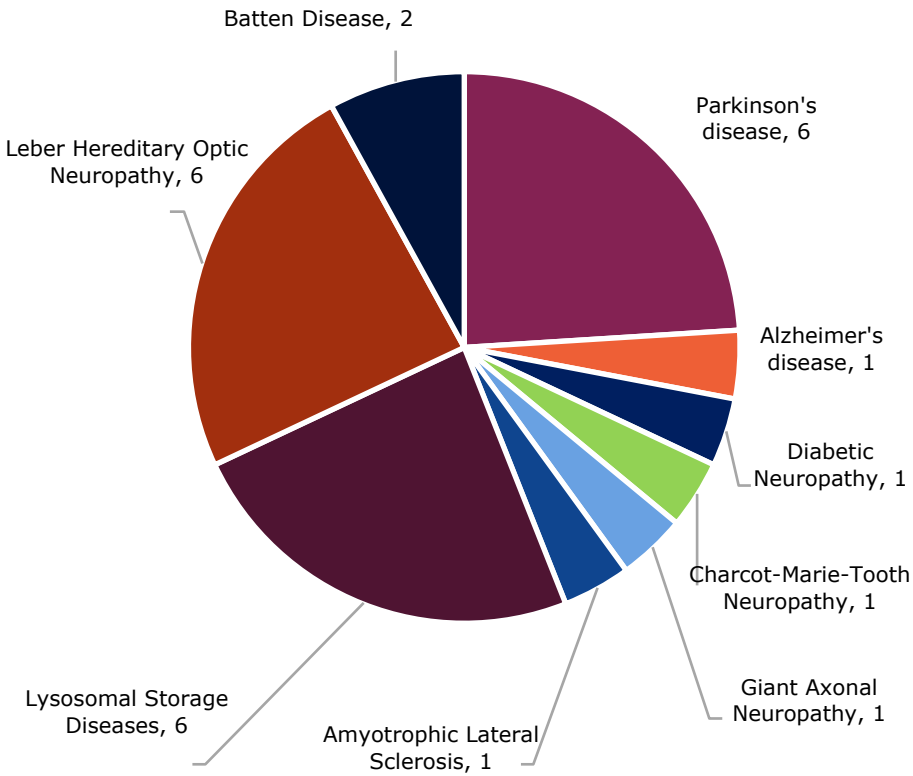
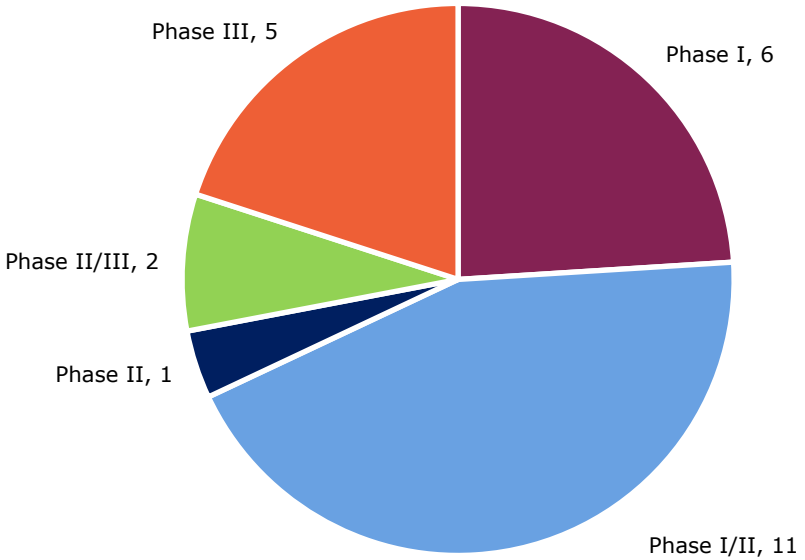
By Indication



By Phase



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+

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Company	Product	Technology	Indication	Clinical Stage	Expected Reporting Date
Orchard Therapeutics	OTL-200	Gene therapy	Metachromatic leukodystrophy	MAA filing, BLA submission	Anticipates filing BLA, MAA in 2020
bluebird bio	Lenti-D	Gene therapy	Cerebral Adrenoleukodystrophy	Ph III	Ph III study to be initiated in 2019
Brainstorm Tx	NurOwn	Mesenchymal Stem Cell Therapy	ALS	Ph III	Enrollment to be completed by mid-2019
GenSight Biologics	GS010	AAV-vector Gene Therapy	Leber Hereditary Optic Neuropathy	Ph III (REVERSE & RESCUE)	Additional data expected Q1 2019; MAA filing expected in Europe in 2019 and in the U.S. in 2020
Axovant	AXO-Lenti-PD	Gene therapy	Parkinson's disease	Ph I/II	Initial data from Cohort 1 expected 1H 2019
Kadimastem	AstroRx	Astrocyte cell therapy	ALS	Ph I/IIa	Initial data from Cohort A expected mid-2019
BlueRock Therapeutics	Undisclosed	iPSC cell therapy	Parkinson's disease	IND submission	IND to be submitted in 2018; first patient treated EOY 2018
uniQure	AMT-130	AAV Gene Therapy	Huntington's disease	IND submission	IND submission in EOY 2018; begin dosing 2019
AveXis	AVXS-201	Gene therapy	Genetic ALS (SOD1)	Pre-IND	IND submission expected in late 2018/early 2019
PTC Therapeutics	Undisclosed	Gene therapy	Friedreich ataxia	pre-IND	Expected to submit IND in 2019

Full list available on ARM's website: https://alliancerm.org/anticipated-data-events/
Source: Company-provided or publicly-available information

Global Financings

$2.8B
Q3 2018

Total Global Financings
(all technologies)

59%
increase from
Q3 2017 YoY

$10.7B
YTD 2018

Total Global Financings
(all technologies)

40%
increase YoY

$2.1B
Q3 2018

Total Gene-Based
Therapies Financings

35%
increase from
Q3 2017 YoY

$7.8B
YTD 2018

Total Gene-Based
Therapies Financings

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

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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!

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