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CHICAGO ILLINOIS

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athn™
american thrombosis & hemostasis network

Gene Therapy Clinical Pipeline

Sector Overview

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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

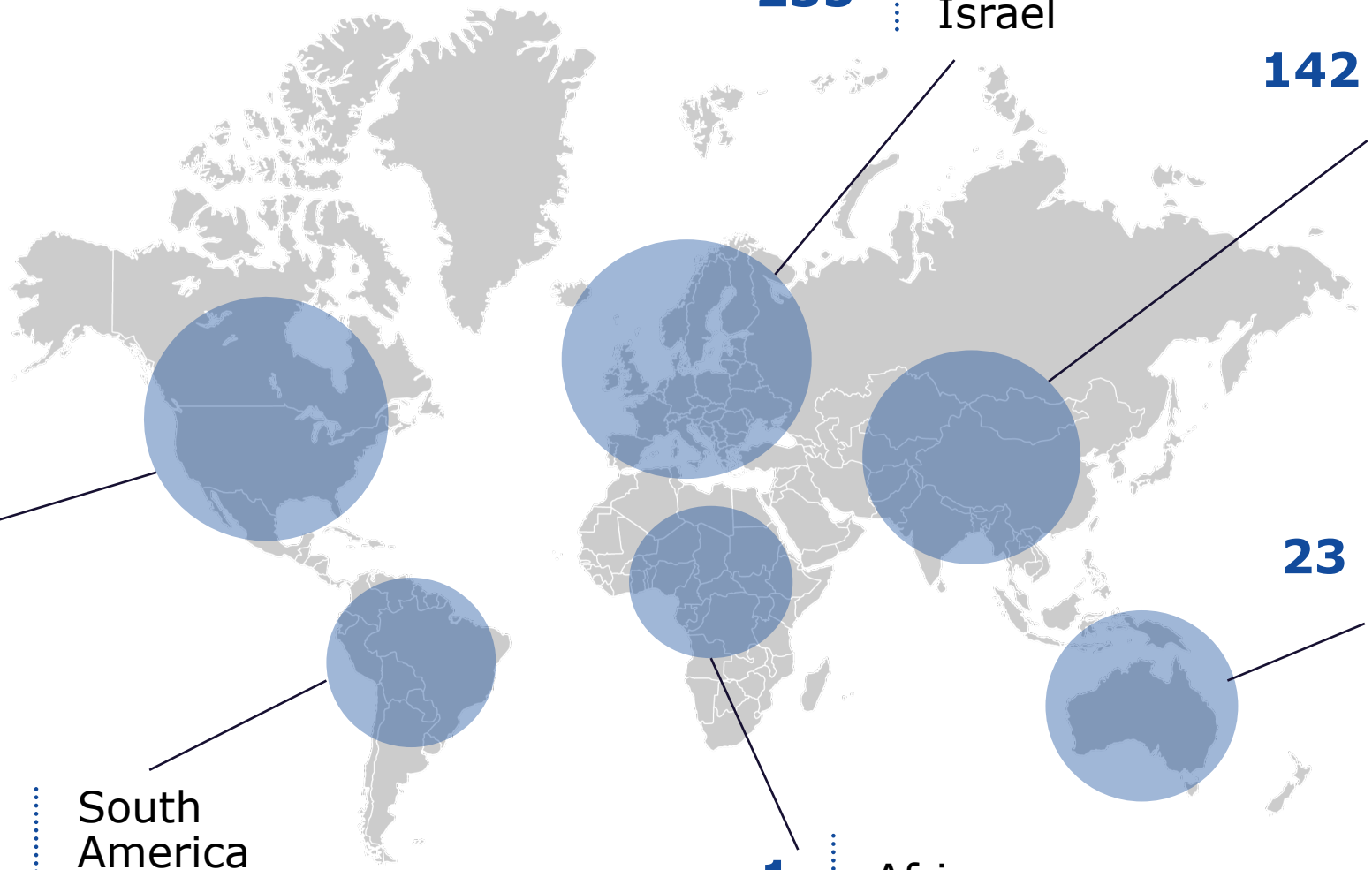
A Quick Note -

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

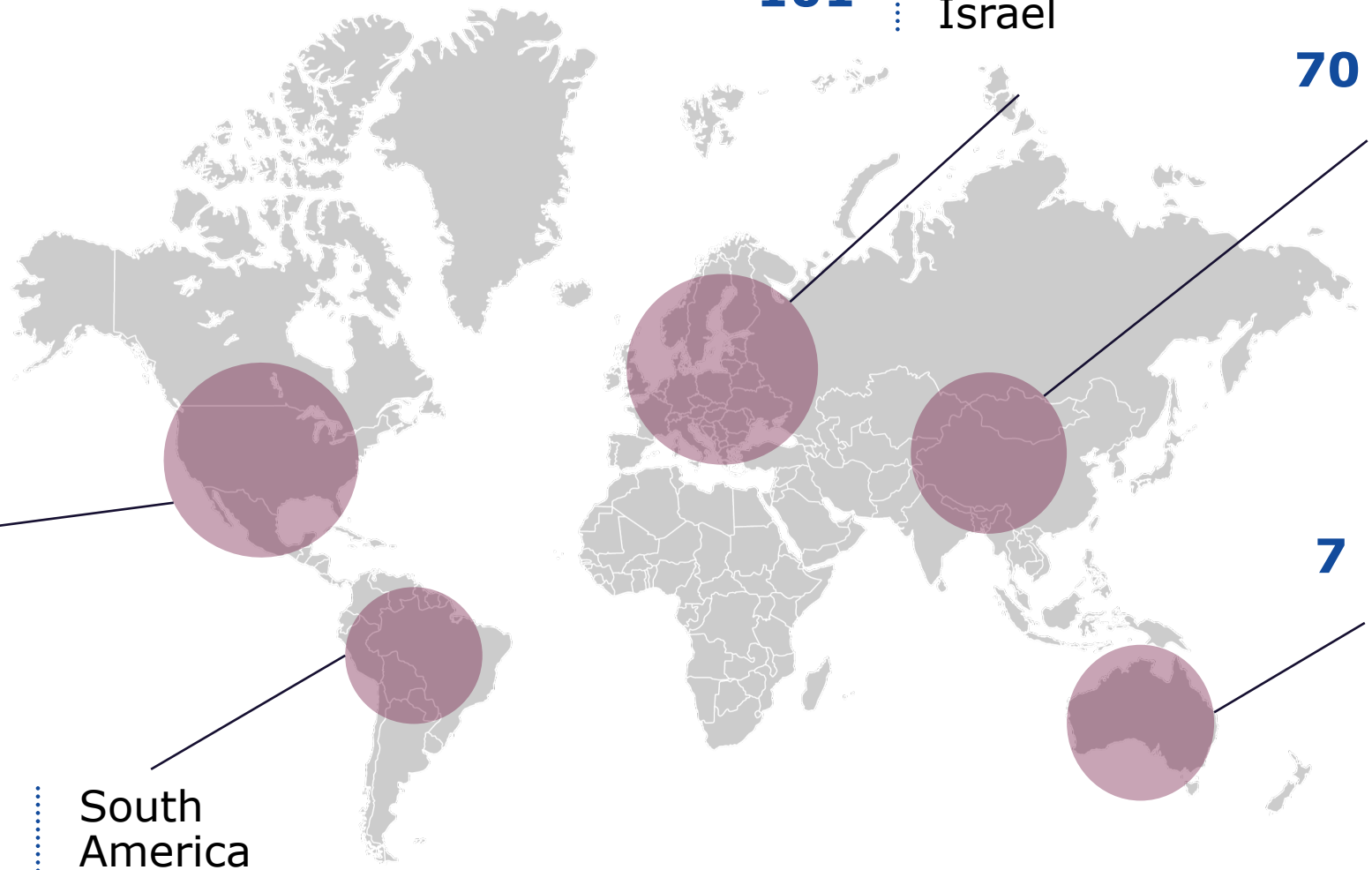
15 South America

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

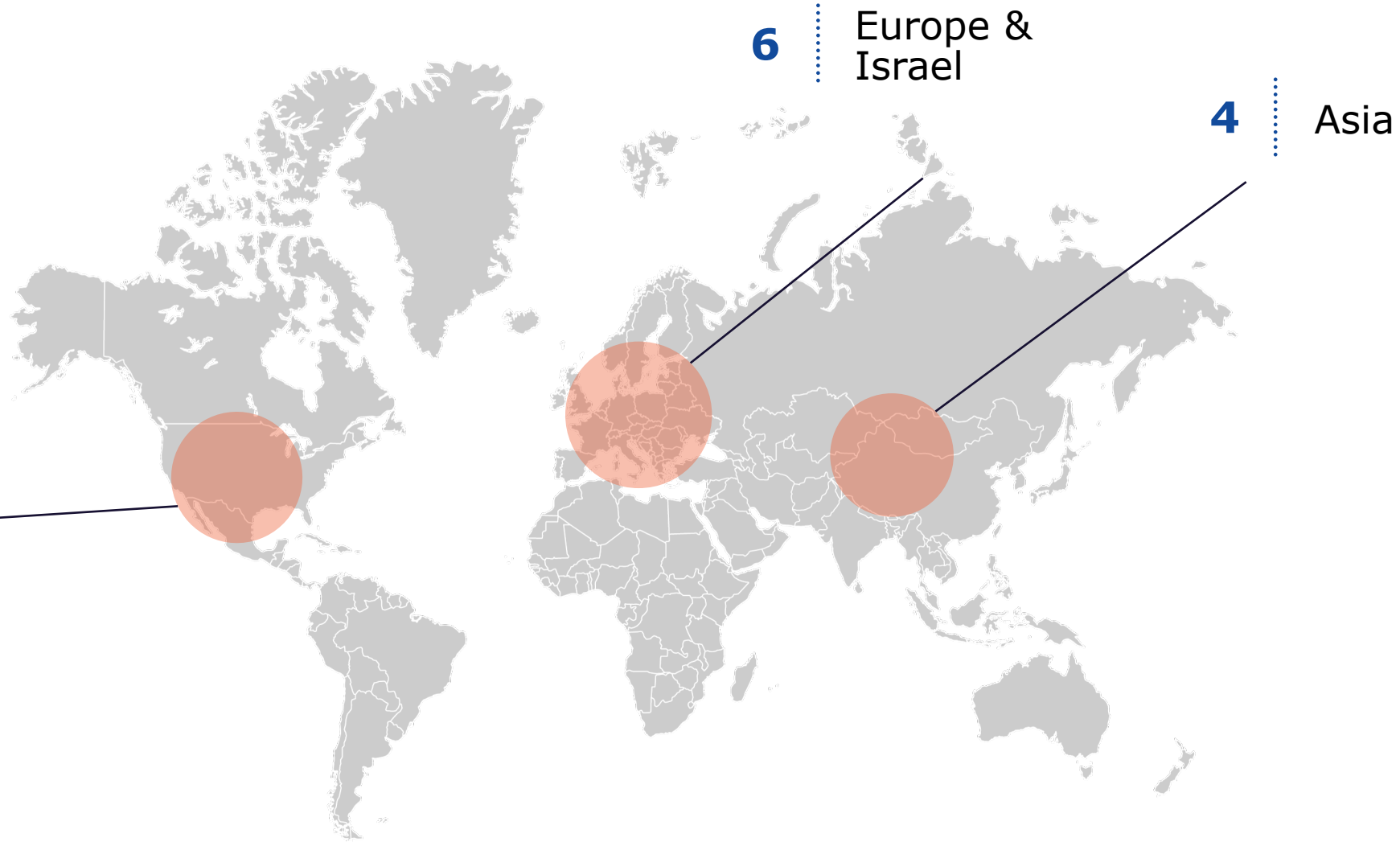
7 Oceania
Australia, New Zealand, Marshall Islands

2 South America

Source data provided by: informa

Current Global Sector Landscape

26
Gene Therapy & Gene-Based Medicine Companies Active in Hematological Indications



Source data provided by: informa

Significant Therapeutic Developers in Hematological Gene Therapy

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Clinical stage:

- Bayer
- BioMarin
- bluebird bio
- CRISPR Therapeutics
- Orchard Therapeutics
- Pfizer
- Rocket Pharma
- Sangamo Therapeutics Inc
- Shire (Baxalta)
- Spark
- Ultragenyx (Dimension acquisition)
- uniQure NV
- Vertex Pharma

Pre-clinical:

- Abeona Therapeutics Inc
- Amarna Therapeutics
- Bioverativ / San Raffaele
- CellGenTech Inc
- CRISPR Tx / Casebia / Maxcyte
- CRISPR Tx / Vertex Pharma
- Editas
- ToolGen Inc / Gene Therapy Research Institution Co Ltd
- Immusoft Corporation
- Poseida Therapeutics Inc
- PROMETHERA Biosciences
- Rocket Pharmaceuticals Inc
- Sangamo Tx / Bioverativ (Sanofi)
- uniQure NV

Major Gene-Based Therapeutic Platforms & Enabling Technologies

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- **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 & 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 in Hematological Indications

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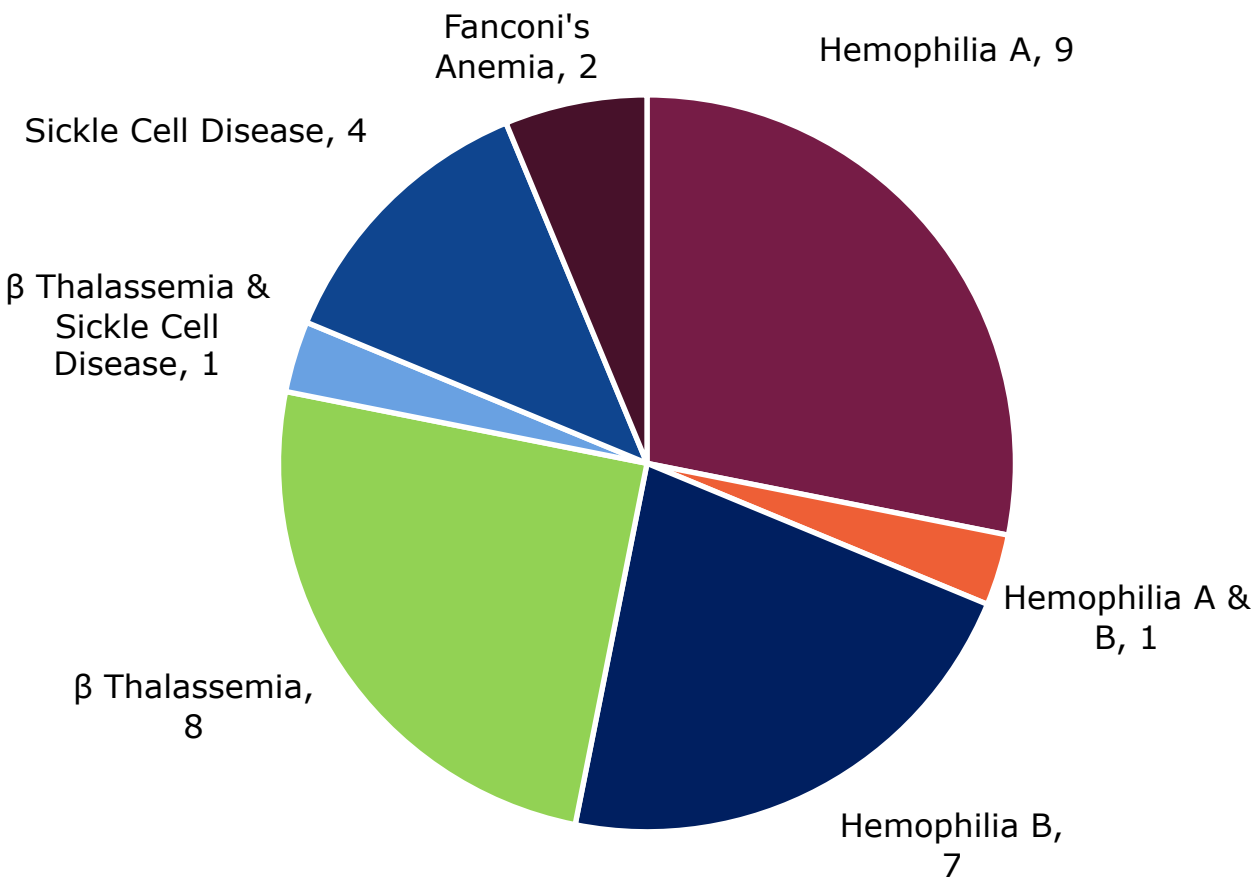
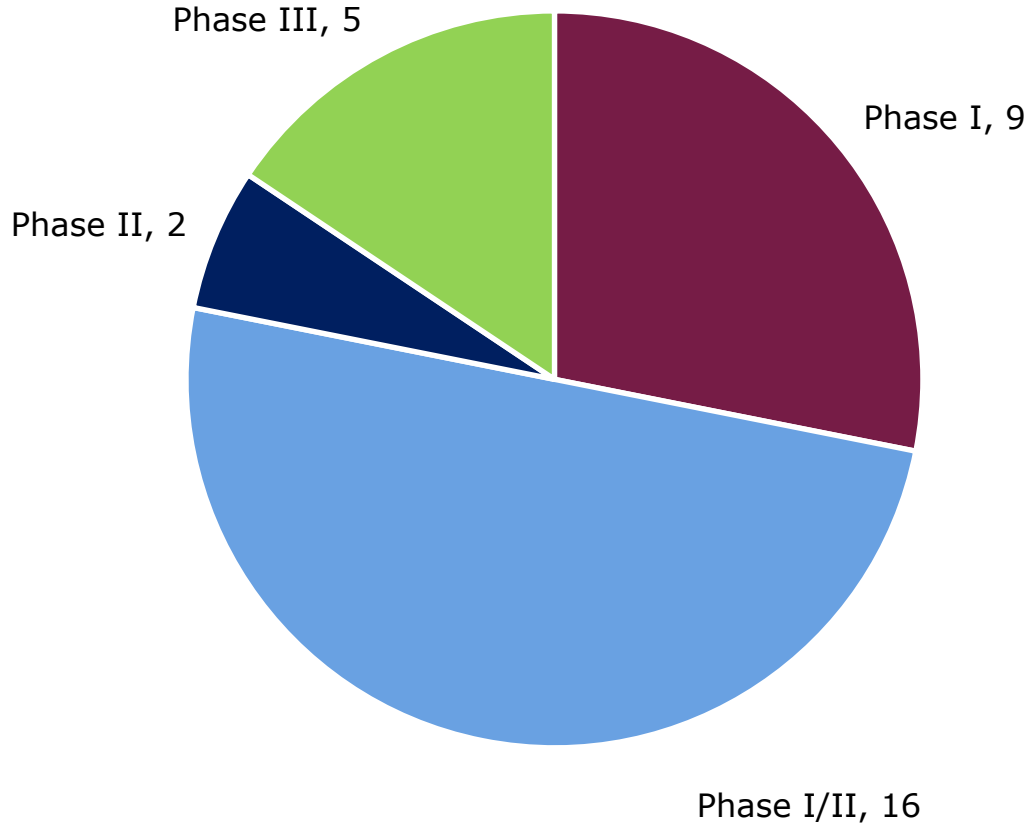
By Indication



By Phase



Approved Products & Select Late-Stage Product Candidates

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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

Currently undergoing assessment:

- bluebird bio's **LentiGlobin** gene therapy for the treatment of adolescents and adults with transfusion-dependent β-thalassemia
  - EMA accepted MAA in October 2018; expected decision in 2019

Select Anticipated Hematological Clinical Data & Events: 2018+

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Company	Product	Vector	Indication	Clinical Stage	Expected Reporting Date
bluebird bio	Lentiglobin	Gene therapy	Transfusion dependent beta-thalassemia	MAA filing	Submitted MAA in 2H 2018; response expected 2019
BioMarin	Valoctocogene roxaparvovec	Gene therapy	Hemophilia A	Ph III	Increase in enrollment to 130 participants anticipated by 1Q 2019
Pfizer	Fidanacogene elaparvovec	Gene therapy	Hemophilia B	Ph III	Initiated trial July 2018
uniQure	AMT-061	Gene Therapy	Hemophilia B	Confirmation study	Topline data from dose confirmation study expected Q4 2018; dosing of patients expected to start early 2019
Sangamo	SB-525	Gene Therapy	Hemophilia A	Ph I/II	Positive preliminary data reported in August 2018
Sangamo	SB-FIX	Genome Editing	Hemophilia B	Ph I/II	UK clinical sites to be set up 2018; currently screening patients in US
CRISPR Tx/Vertex	CTX001	Autologous gene-edited hematopoietic stem cell therapy	Transfusion dependent β-thalassemia & sickle cell disease	Ph I/II	Expected to initiate in 2h 2018
Spark Therapeutics	SPK-8011	AAV-vector gene therapy	Hemophilia A	Ph I/II	plan to initiate a Phase 3 run-in study in Q4 2018
Bioverativ	BIVV003	Gene-edited cell therapy	Sickle cell disease	Pre-Ph I	Received IND approval in May 2018; expected to open clinical sites later this year

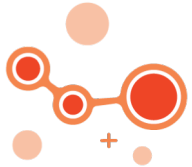
Source: Company-provided or publicly-available information

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

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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.
- 27 products have received the designation (as of Oct. 2018) – 22 have announced publicly

6 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. Nightstar Tx's NSR-REP1 (choroideremia)
6. 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 Hemophilia**:
      - Discusses considerations for trial sponsors, including the use of surrogate endpoints, dosage of prophylactic replacement therapy prior to the trial, use of prophylactic replacement therapy post administration, study population, monitoring factor activity levels post-administration, and the use of patient experience data
    - 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

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 hematology and overall
- Significant near-term late-stage anticipated clinical milestones, including multiple late-stage trials for hematological disorders

Sustained investor, partnering interest:

- Substantial year-over-year increases in investment and financings overall and in gene-based therapies

Commercial opportunities and challenges:

- Transformative products 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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