

# ATMPs in Europe

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## State of Play

**Annie Hubert, Senior Director European Public Policy,  
Alliance for Regenerative Medicine**

*6 February 2020 – Cell And Gene Therapy Innovation Summit, Berlin*



## About ARM

- **International advocacy organization**
  - Dedicated to realizing the promise of safe and effective regenerative medicines for patients around the world
  - Cell and gene therapy, tissue engineering
- **350+ members**
  - Small and large companies, non-profit research institutions, patient organizations, and other sector stakeholders
  - Across 25 countries
- **Priorities:**
  - Clear, predictable, and harmonized **regulatory** pathways
  - Enabling market access and value-based **reimbursement** policies
  - Addressing industrialization and **manufacturing** hurdles
  - Compile sector data, **educate** media and other stakeholders

# 350+ ARM Members

*\*\*Members in bold are publicly traded companies*



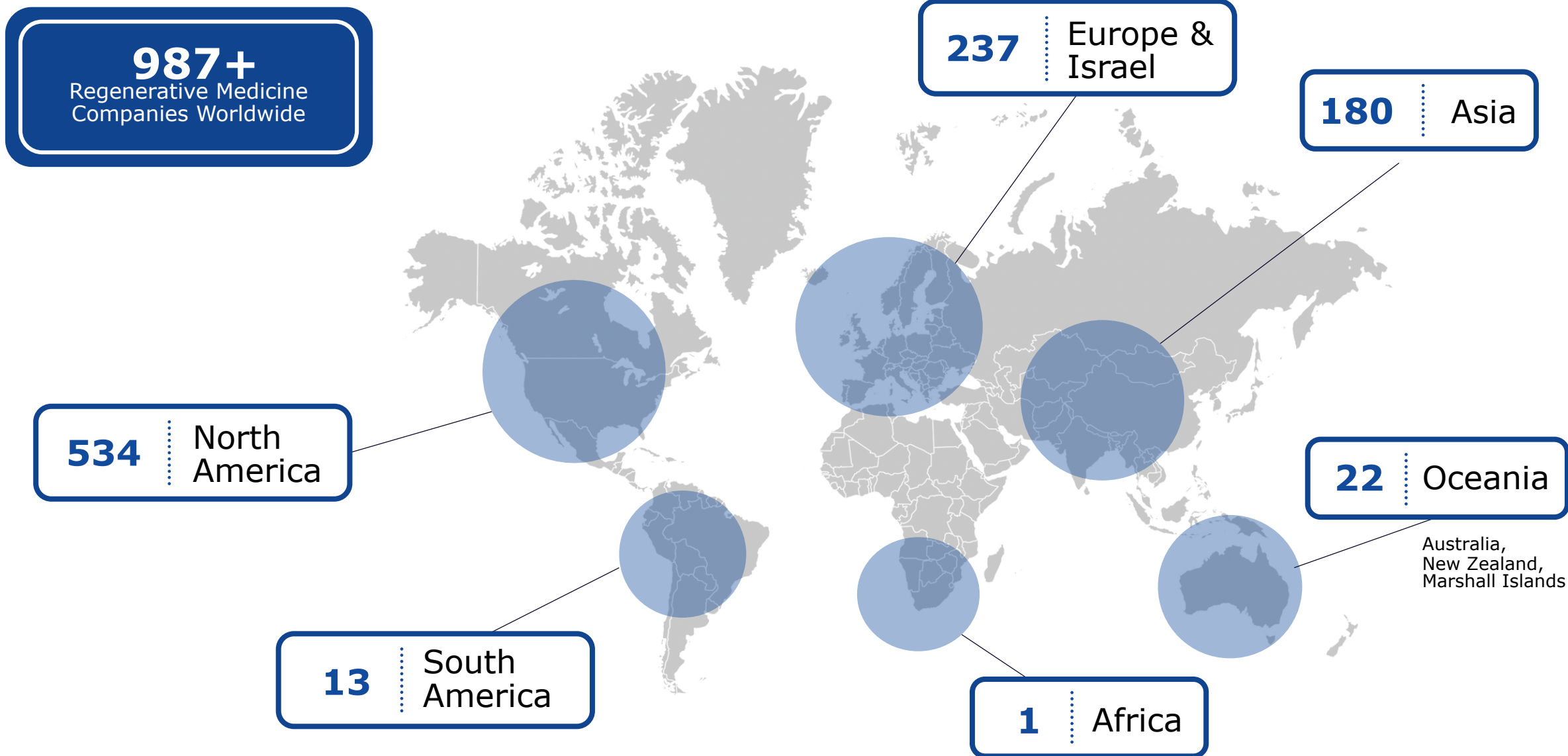
4BIO Capital 4D Molecular Tx AABB **Abeona Tx** Accelerated Bio ACF Bioservices **Adaptimmune** Adicet Bio **Adverum Bio** **AGTC** Aivita Biomedical Akouos Akron Bio Alumedix Aldevron Alpha-1 Foundation Ambys American Association of Tissue Banks American Gene Technologies International American Society of Plastic Surgeons **Amicus** Andalusian Initiative for Advanced Therapies ANEMOCYTE Angiocrine Bio apceth Biopharma Archbow Consulting Artiva Bio Aruvant Aseptic Technologies ASGCT AskBio Aspect Biosystems Asset Management Company Association of Clinical Research Organizations **Astellas Atara Bio Athersys** **Audentes Tx** AusBiotech **Autolus** Avectas Avery Tx **Avita Medical** AVM Bio **AVROBIO** **AxoGen** **Axovant** B-MoGen Barkey Baylor College of Medicine Be the Match Biotherapies Beam Tx **Bellicum Pharma** BioBridge Global **BioCardia** **BioLife Solutions** **BioMarin** **BioStage** Biotech Mountains Blood Centers of America **bluebird bio** BlueRock Tx **Bone Tx** **BrainStorm Cell Tx** Brainxell Brammer Bio C3i **Cabaletta Bio** **Caladrius Bio** **Capricor Tx** **Cardinal Health** Caribou Bio Carisma Carpenter Consulting Cartherics Celavie Bio **Celgene (BMS)** CEO Council for Growth CGT Catapult Cell Medica Cellatoz CellCAN **Collect Bio** CellGenix Cello Health **CBMG** Cellular Technology Limited Celonic Celsense Center for the Advancement of Science in Space CCRM Century Tx Cevec Chemelot CIRM City of Hope Cleveland Clinic Cleveland Cord Blood Center ClinicalMind Coalition for Clinical Trials Awareness Cobra Bio Cognate Bio **CombiGene** Cook Myosite Cornell University Covance **CRISPR Tx** **Cryoport Systems** **CSL** CTI Clinical Trial and Consulting Services CureDuchenne **Cynata Tx** Dark Horse Consulting DiscGenics EB Research Partnership **Editas Medicine** Elevate Bio Emerging Therapy Solutions Encoded Tx Enzyvant Tx ERA Consulting ESGCT EVERSANA EveryLife Foundation for Rare Diseases Evidera ExCellThera Exogrades Falcon Tx FARA **Fate Tx** **Fibrocell Science** Fight Colorectal Cancer **Flexion Tx** Fondazione Telethon Foundation for Biomedical Research and Innovation Fraunhofer Institute for Cell Therapy and Immunology Fred Hutchinson Cancer Research Center Frequency Tx **Fresenius Kabi** **FUJIFILM Cellular Dynamics** G-CON Manufacturing GalbraithWight **Gamida Cell** GammaDelta Tx G-CON Manufacturing **GE Healthcare** GE2P2 Global Foundation Gemini BioProducts Generation Bio GENETHON **Genprex** **GenSight Biologics** Gift of Life Marrow Registry **Gilead / Kite** Giner **GlaxoSmithKline** Global Genes GPB Scientific Gyroscope Tx Halloran Consulting **Healios K.K.** Histogen **Hitachi Chemical** **Advanced Tx Solutions** Hogan Lovells **Homology Medicines** Humanscape Huron Consulting Hybrid Concepts International ICON Immusoft InRegen InsightRX **Intellia Tx** Invetech Invitria Invitrx **Iovance** **IQVIA** ISCT ISSCR **IVERIC Bio** Johns Hopkins **Johnson & Johnson** Key Biologics **Kiadis Pharma** Kimera Labs Kytopen L7 Informatics LabConnect Lake Street Capital Markets Latham BioPharma LatticePoint Consulting Legend Biotech Locate Bio LogicBio **Lonza Biologics** Lovelace Biomedical Ludwig Boltzmann Institute **Lysogene** **Magenta Tx** Mammoth Bio MaSTherCell **MaxCyte** MEDIPOST America **Medpace** **MeiraGTx** MSK Cancer Center **Mesoblast** **Limited MilliporeSigma** **MiMedx** Minerva Bio Miromatrix Medical Missouri Cures **MolMed** Musculoskeletal Transplant Foundation **Mustang Bio** National Disease Research Interchange National Multiple Sclerosis Society National Stem Cell Foundation Nebraska Coalition for Lifesaving Cures NeoProgen Neural Stem Cell Institute Neurogene New Jersey Innovation Institute New York Stem Cell Foundation NexImmune NIIMBL Nkarta Northwestern University Comprehensive Transplant Center Novadip Bio **Novartis / Avexis** Novitas Capital **Novo Nordisk** NYBC Obsidian Odylia Tx OIRM Oisin Bio OncoSenX Opsis Tx **Orchard Tx** Organabio **Orgenesis** Orig3n **Oxford BioMedica** panCELLa Parent Project Muscular Dystrophy PDC\*line Pharma SA **Pfizer** **Pluristem Tx** **PolarityTE** Polyplus-transfection **Poseida Tx** Precigen **Precision Bio** **Prevail Tx** Prevent Cancer Foundation Project 8p Project Farma Promethera Bio **PTC Tx** Recardio Recombinetics Regenerative Patch Technologies ReGenesys **Regeneus** REGENXBIO REMEDI ReNeuron Replicel Life Sciences Rescue Hearing Rexgenero Rigenrand **Rocket Pharma** RoosterBio Roslin CT Rousselot RxGen **SanBio** Sanford Health Sanford Stem Cell Clinical Center @ UCSD **Sangamo Tx** **Sanofi** **Sarepta** Sartorius Stedim North America SCM LifeScience Scottish National Blood Transfusion Service Semma Tx Seneca Bio Senti Biosciences Sentien Bio Seraxis Sernova Sigilon Sirion Biotech Skyland Analytics SmartPharm Tx **Solid Bio** **Spark Tx** StafaCT Starfish Innovations STEL Technologies StemBioSys StemCyte StemExpress Stempeutics Stop ALD Foundation Student Society for Stem Cell Research Sven Kili Consulting Synpromics T-Knife Tacitus Tx **Takeda** Talaris Tx Tenaya TERMIS-Americas Terumo BCT Tessa Tx Texas Heart Institute The Michael J. Fox Foundation Theradaptive **Thermo Fisher Scientific** **ThermoGenesis** TikoMed Tmunity Tx TrakCel TreeFrog Tx Tremont Tx LLC Trizell Tulane University UCSD Stem Cell Program **Ultragenyx** UMass Medical School Unicyte **uniQure** Unite 2 Fight Paralysis United Spinal Association of VA Universidad de los Andes University of Colorado University of Pennsylvania **Unum Tx** VERIGRAFT ViaCyte VidaCel Videregen Vigene VINETI ViveBiotech Vivet Tx Voisin Consulting **Voyager Tx** WiCell WindMIL Tx World Courier **Wuxi** **Xintela** Xyphos Bio Yposkesi Zelluna **Ziopharm Oncology**

# Sector Landscape Overview

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- ✓ *Continued growth of the sector*
- ✓ *US remains the main center of activity*
- ✓ *Europe continues to constitute a quarter of the sector*
- ✓ *The most recent approved products have a profound impact on patients*

# Current Global Sector Landscape



# European Sector Landscape

**237+**

Regenerative Medicine  
Companies HQ'd in Europe



*Nearly ¼ of regenerative  
medicine therapeutic developers  
are headquartered in Europe*



**24**

ATMPs Granted RMAT,  
PRIME, and/or SAKIGAKE  
Designations in 2019



**1,066**

Ongoing ATMP  
Clinical Trials



**€8.8B**

Raised in Global  
Financings in 2019

***2019 has been a significant year of growth for the  
regenerative medicine sector***



**10**

ATMPs Granted PRIME  
Designation in 2019



**260**

Ongoing ATMP  
Clinical Trials



**€2.7B**

Raised in Global  
Financings in 2019

***2019 has been a significant year of growth for the  
advanced therapies sector in Europe***



# Patient Impact of Recently Approved Products in Europe

Therapy Name	Product Developer	Response
<b>Zynteglo</b>	bluebird bio	<ul style="list-style-type: none"> <li><b>75%</b> of patients with TDT without <math>\beta 0/\beta 0</math> genotype treated achieved transfusion independence</li> </ul>
<b>LUXTURNA</b>	Spark Therapeutics	<ul style="list-style-type: none"> <li><b>93%</b> of patients treated showed an improvement of at least 1 light level from baseline</li> </ul>
<b>Yescarta</b>	Kite Pharma, a Gilead company	<ul style="list-style-type: none"> <li><b>58%</b> of patients with R/R B-Cell NHL treated experienced a complete response</li> </ul>
<b>Kymriah</b>	Novartis	<ul style="list-style-type: none"> <li><b>40%</b> of patients with R/R DLBCL treated experienced a complete response</li> <li><b>82%</b> of patients with R/R B-Cell ALL treated experienced complete remission or complete remission with incomplete hematologic recovery</li> </ul>



# Select Anticipated Near-Term Approvals in Europe



## Gene Therapy

### **Zolgensma** (AveXis / Novartis)

- Spinal muscular atrophy type 1
- Filed for approval in the EU mid-2019

### **ValRox** (BioMarin)

- Severe hemophilia A
- Filed for approval in the EU in December 2019

### **OTL-200** (Orchard Therapeutics)

- Metachromatic leukodystrophy
- Filed for approval in the EU in December 2019

### **PTC-AADC** (PTC Therapeutics)

- AADC deficiency
- Filed for approval in the EU in January 2020

### **AT132** (Audentes / Astellas)

- Metachromatic leukodystrophy
- Expects to file in the EU in 2H 2020

### **Lent-D product** (bluebird bio)

- Cerebral adrenoleukodystrophy
- Expects to file in the EU in 2H 2020

### **GS010** (GenSight Biologics)

- Leber hereditary optic neuropathy
- Expects to file in the EU in 2H 2020



## Cell-Based Immuno-Oncology

### **KTE-X19** (Kite Pharma / Gilead)

- Relapsed or refractory mantle cell lymphoma
- Filed for approval in the EU in December 2019

# Scientific & Clinical Advances

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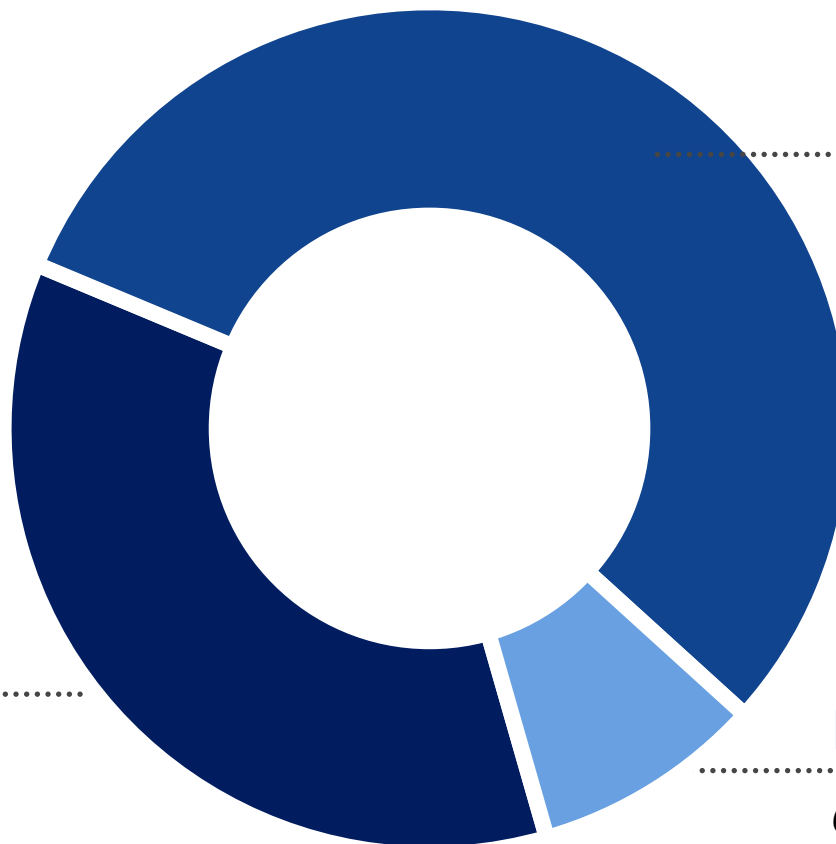
- ✓ *Substantial late stage clinical activity*
- ✓ *Explosion of gene-modified cell therapies, including allogeneic GMCTs and GMCT trials in immunology*
- ✓ *Increasing clinical activity in diverse and more prevalent indications*
- ✓ *Advances in somatic cell gene editing*
- ✓ *Advances in viral and non-viral gene delivery methods for gene therapies*

# The Global Clinical Landscape for ATMPs

**1,066**  
Ongoing ATMP  
Clinical Trials

## Phase 1: 381

*Gene Therapy: 111*  
*Gene-Modified Cell Therapy: 222*  
*Cell Therapy: 42*  
*Tissue Engineering: 6*



## Phase 2: 591

*Gene Therapy: 209*  
*Gene-Modified Cell Therapy: 215*  
*Cell Therapy: 144*  
*Tissue Engineering: 23*

## Phase 3: 94

*Gene Therapy: 32*  
*Gene-Modified Cell Therapy: 15*  
*Cell Therapy: 30*  
*Tissue Engineering: 17*

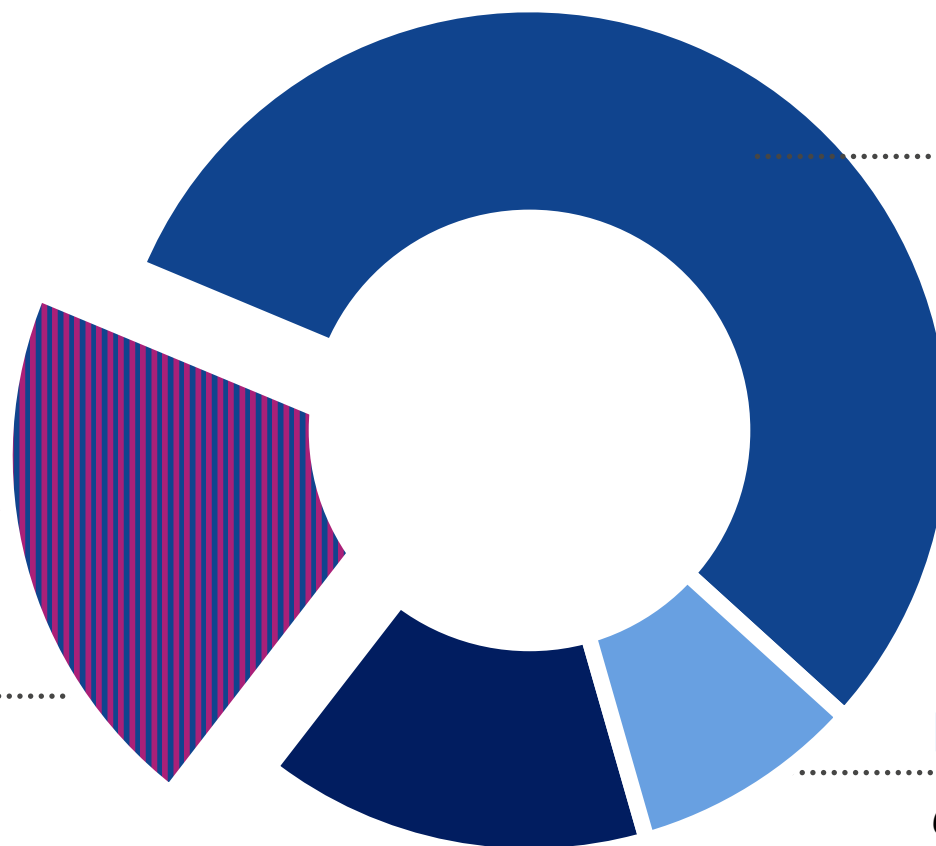
# The Global Clinical Landscape for ATMPs

**58%**

of Phase 1 Trials are  
in gene-modified cell  
therapies

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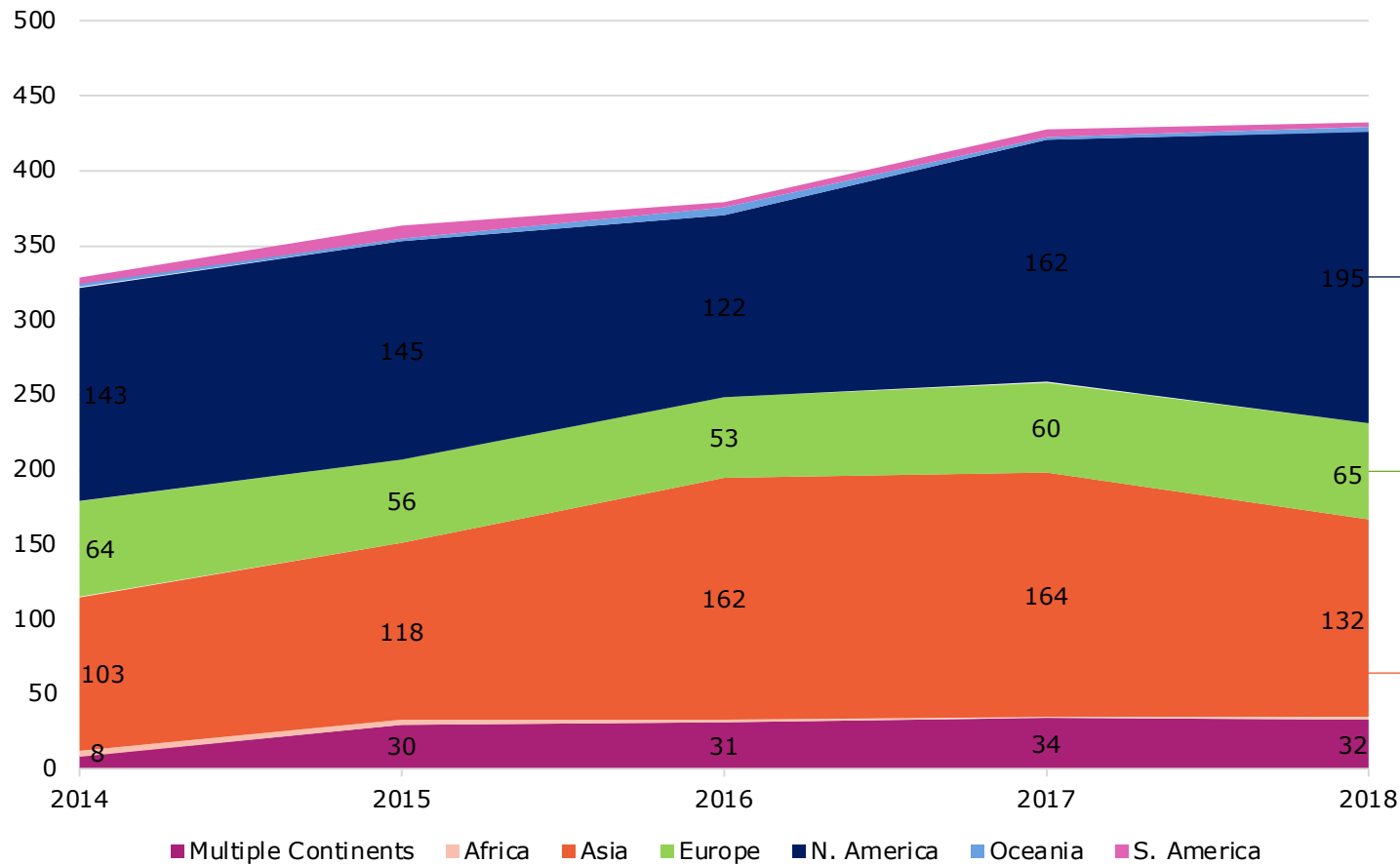
## Phase 3: 94

*Gene Therapy: 32*  
*Gene-Modified Cell Therapy: 15*  
*Cell Therapy: 30*  
*Tissue Engineering: 17*

# Global Comparative Clinical Development

*The growth of new ATMP clinical trials is significantly lower in Europe than in other regions.*

## New ATMP Clinical Trials by Region



**Growth, 2014 to 2018**  
↑32% Globally

N. America: ↑36%

Europe: ↑2%

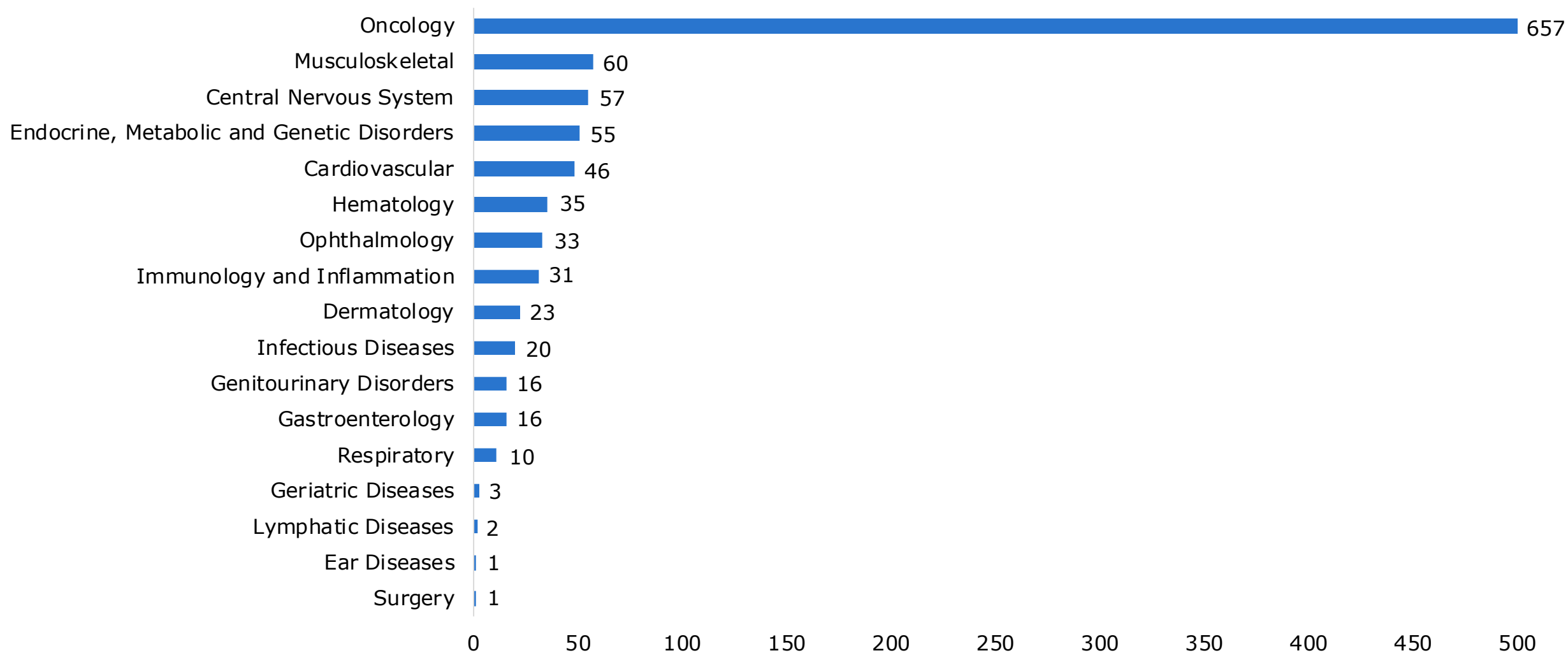
Asia: ↑28%

Total new trials started during the 2014-2018 period = 2,097

(All new trials started in more than 1 continent are under Multiple Continents category)

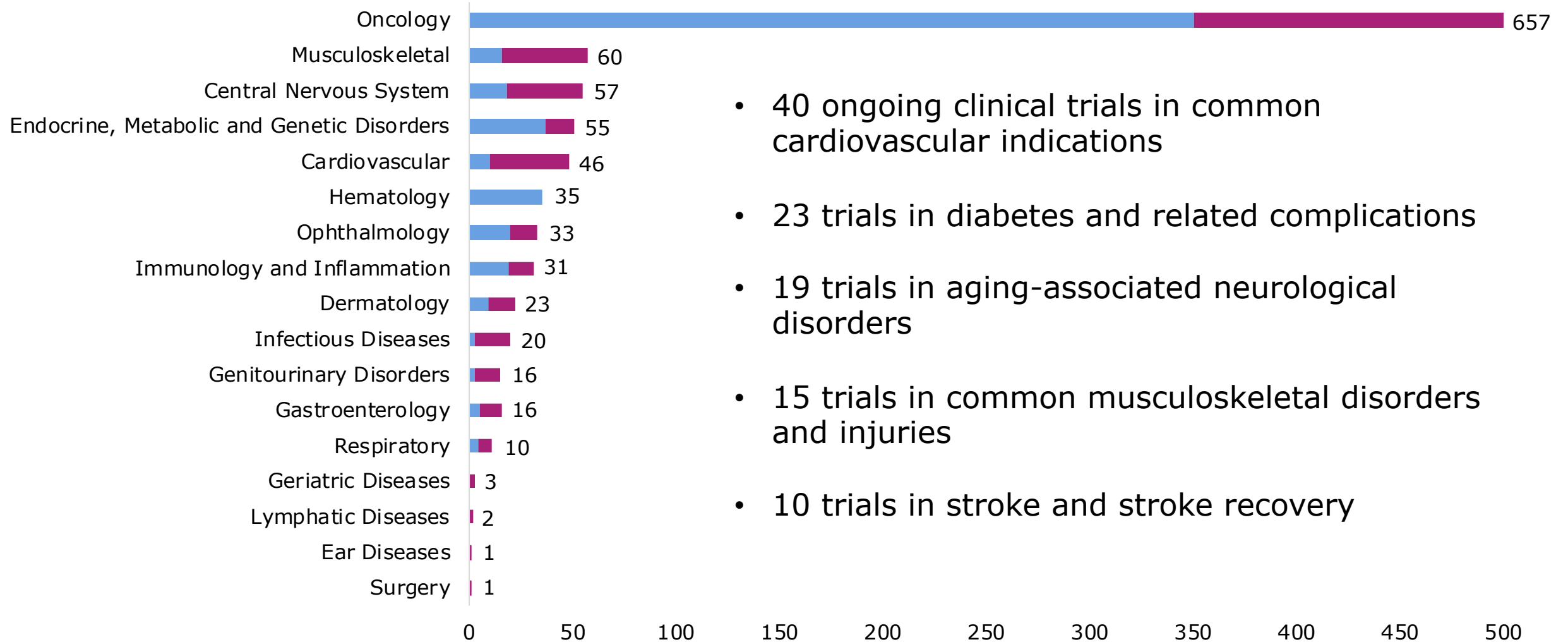
Source: [ARM Report on Clinical Trials in Europe, Recent Trends in ATMP Development](#), October 2019

# Clinical Trials Across Diverse Indications



# Increasing Clinical Activity in Larger Indications

*More prevalent indications indicated in purple*



- 40 ongoing clinical trials in common cardiovascular indications
- 23 trials in diabetes and related complications
- 19 trials in aging-associated neurological disorders
- 15 trials in common musculoskeletal disorders and injuries
- 10 trials in stroke and stroke recovery





**Victoria Gray**, the first sickle cell patient in the US to be treated with CRISPR

## 31 ongoing Phase 1 gene editing trials worldwide

- 20 in oncology, 8 in inherited disorders, 3 in HIV
- CRISPR joined ZFNs and TALENs in the clinic
  - First patients treated in trials to treat beta thalassemia, sickle cell (**Vertex/CRISPR**)
  - First patient treated in trial of CRISPR-edited TCR for sarcoma (**Tmunity/PICI/Penn Medicine**)
  - Evidence of successful *in vivo* editing in Phase 1/ 2 Study (**Sangamo**)
  - First *in vivo* CRISPR patient to be treated early this year (**Editas**)
- **Allogene**, **Cellctis**, and **Precision** entered the clinic in 2019 with gene-edited allogeneic CAR-Ts

# Advances in Gene Therapy Delivery

## Researchers drove progress in gene therapy delivery methods:



BU researchers create new protocol to improve gene therapy tool production



**A new gene therapy strategy, courtesy of Mother Nature**  
*Scientists turn a natural cellular process into a drug-delivery system*



NIH researchers create new viral vector for improved gene therapy in sickle cell disease



**NEWS**

Tiny capsules packed with gene-editing tools offer alternative to viral delivery of gene therapy



Johns Hopkins Researchers Advance Search For Safer, Easier Way to Deliver Vision-Saving Gene Therapy to The Retina



*Scripps Research team finds that a nontoxic molecule can overcome barriers to delivering gene therapy into stem cells.*

## Non-viral delivery advancements:

- Japan approved Colletagene, a non-viral gene therapy to treat critical limb ischemia
- There are currently 57 ongoing gene therapy trials utilizing non-viral delivery methods

## Companies are partnering to overcome challenges in gene therapy & gene-modified cell therapy manufacturing:

- Ziopharm Oncology and MD Anderson announced a new R&D agreement to expand TCR-T program
- SQZ Biotech and AskBio announced collaboration to overcome AAV immunogenicity

# Focus on Manufacturing

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- ✓ *In-house manufacturing capabilities often a strategic priority*
- ✓ *Companies invested in manufacturing earlier in the development process*
- ✓ *CMOs were attractive acquisition targets*

# Expanding Manufacturing Capabilities

Numerous companies invested in in-house manufacturing capabilities:



Pfizer, Novartis lead \$2 billion spending spree on gene therapy production

**Bloomberg**

**Kite Announces Plans for New State-of-the-Art Facility to Expand Cell Therapy Production Capabilities**



**BRIEF**

**Thermo Fisher opens \$90M viral vector manufacturing plant in Massachusetts**

# Expanding Manufacturing Capabilities

## Pre-market companies invested in manufacturing early:

AUDENTES 

Audentes announced addition of cGMP plasmid manufacturing to existing large scale AAV operations

 **REGENXBIO**<sup>TM</sup>

REGENXBIO announced new manufacturing facility, to be operational in 2021

**elevatebio** 

ElevateBio launched with \$150M to provide centralized R&D and manufacturing capabilities to suite of CGT developers

 **PRECISION**  
BIOSCIENCES

Precision BioSciences opened first in-house cGMP manufacturing facility dedicated to genome-edited allogeneic CAR-Ts in the US

# Expanding Manufacturing Capabilities

CMOs were attractive acquisition targets in 2019:



Novartis acquires CellforCure to boost CAR-T manufacturing



Hitachi gets EU cell manufacturing facilities with deal to buy Apceth Biopharma



Thermo Fisher to Acquire Brammer Bio for \$1.7B



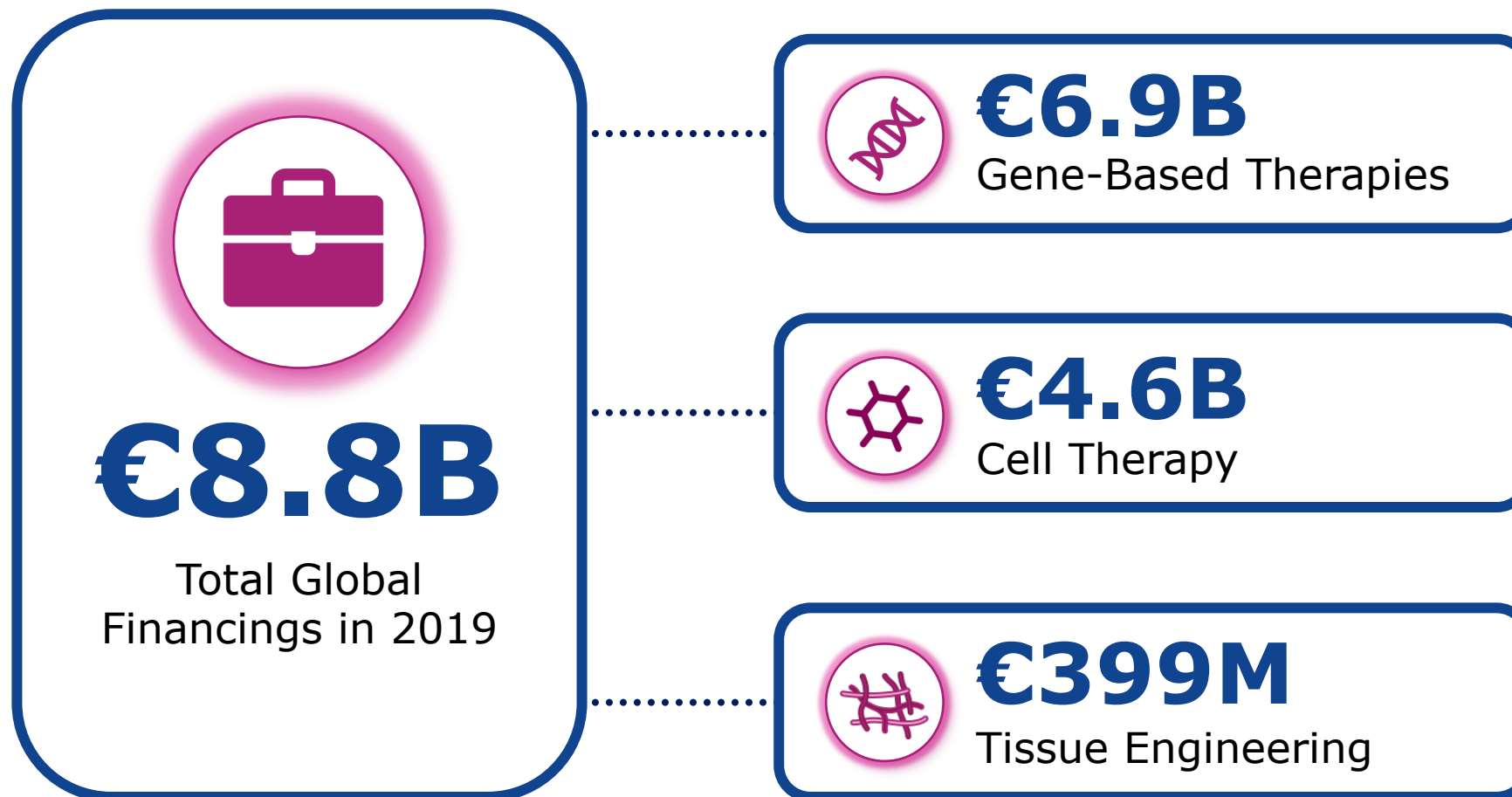
Catalent acquires gene therapy specialist Paragon for \$1.2bn

# Financing Trends

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- ✓ *Total global financings in 2019 second highest ever for the sector*
- ✓ *Strong year for venture financing and corporate partnerships*
- ✓ *Large- and mid-cap pharma company M&A interest in cell & gene therapy*
- ✓ *European companies had a strong year for financings, on par with 2018*

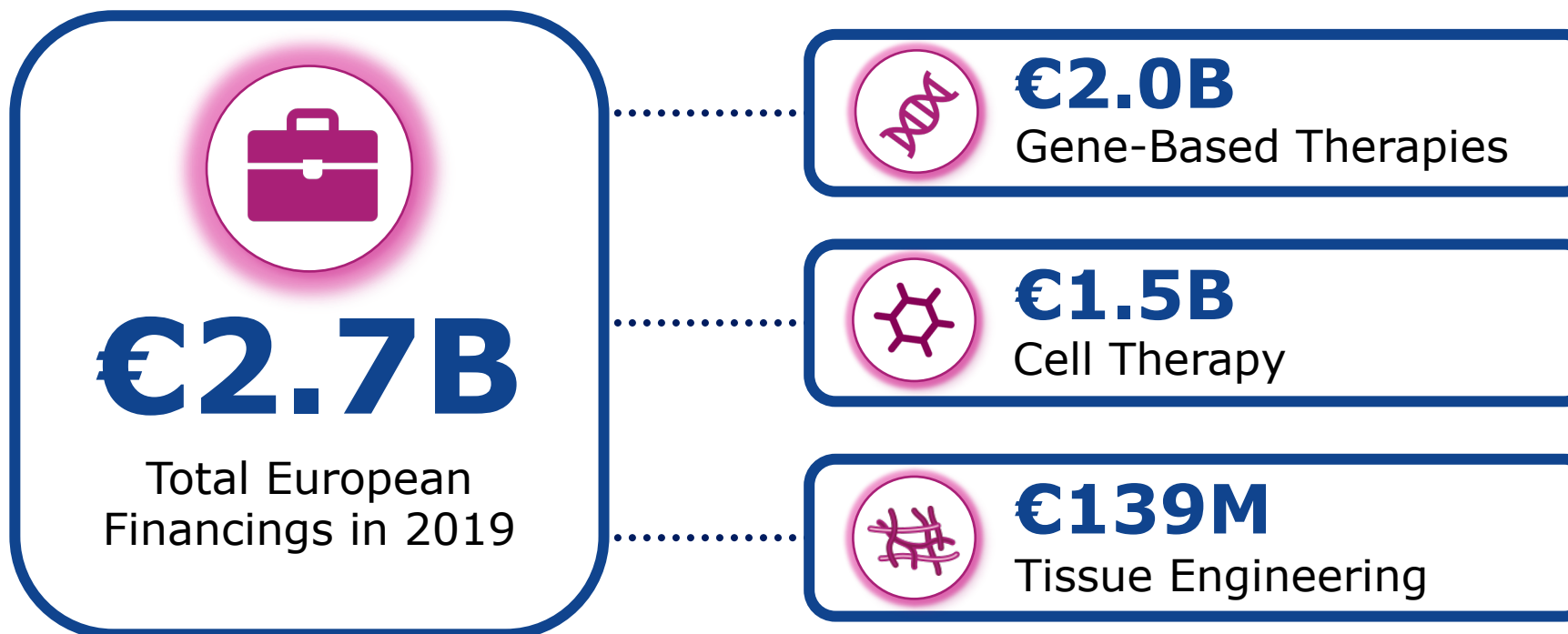
# Total Global Financings 2019



*\*both Gene-Based Therapies & Cell Therapy categories include financings from companies active in developing gene-modified cell therapies – therefore, total financings does not equal the sum of each technology category*



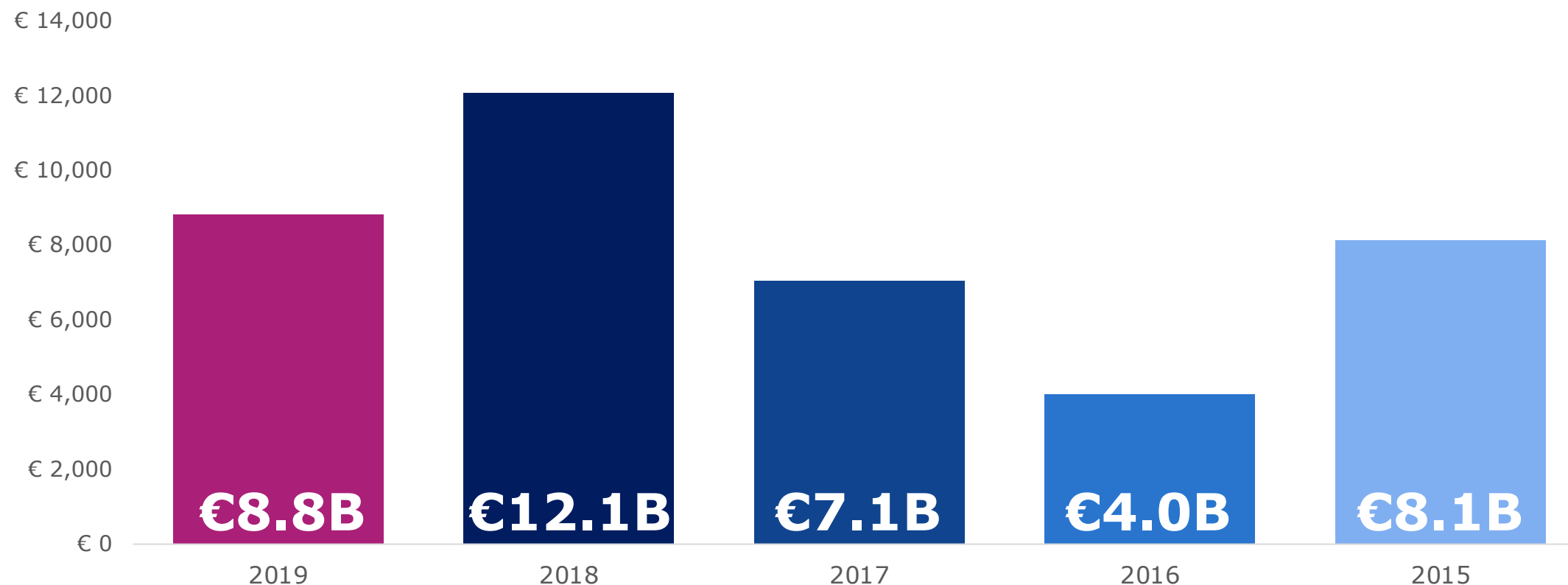
# Total Financings by European-Based Companies in 2019



*Despite YoY decreases in global financings, financings from regenerative medicine companies headquartered in Europe were on par with 2018.*

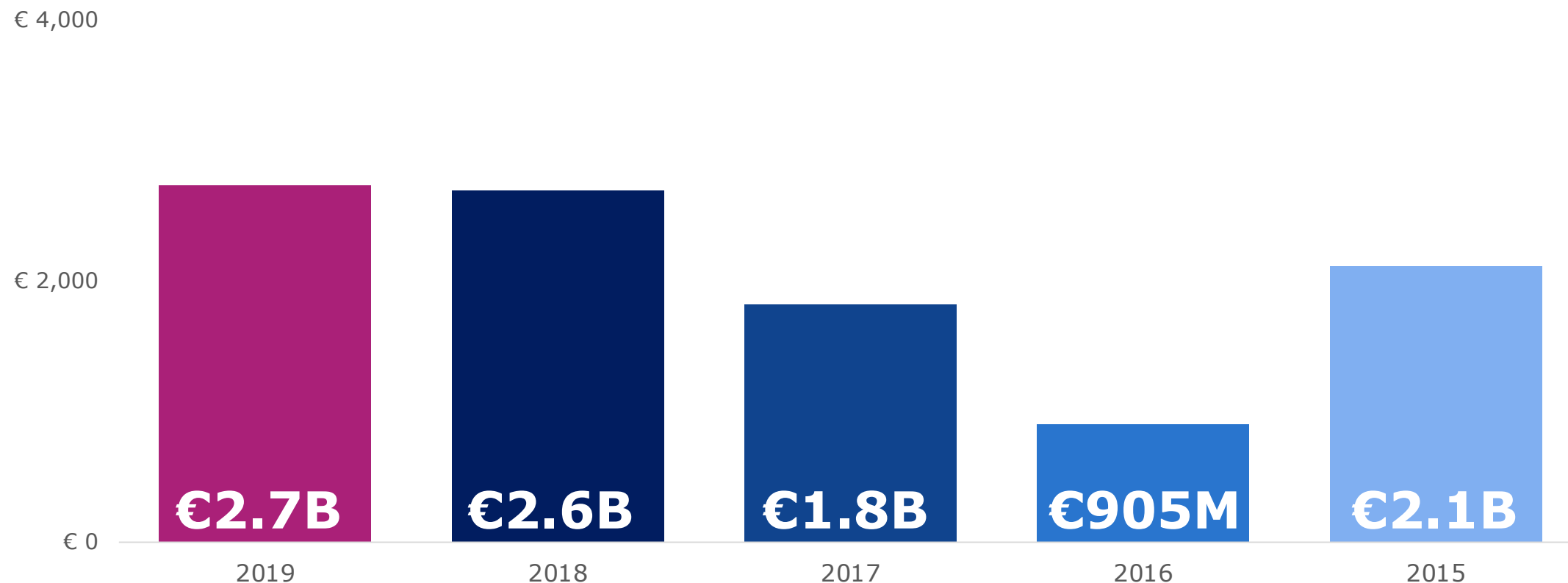
*\*both Gene-Based Therapies & Cell Therapy categories include financings from companies active in developing gene-modified cell therapies – therefore, total financings does not equal the sum of each technology category*

# Total Global Financings by Year



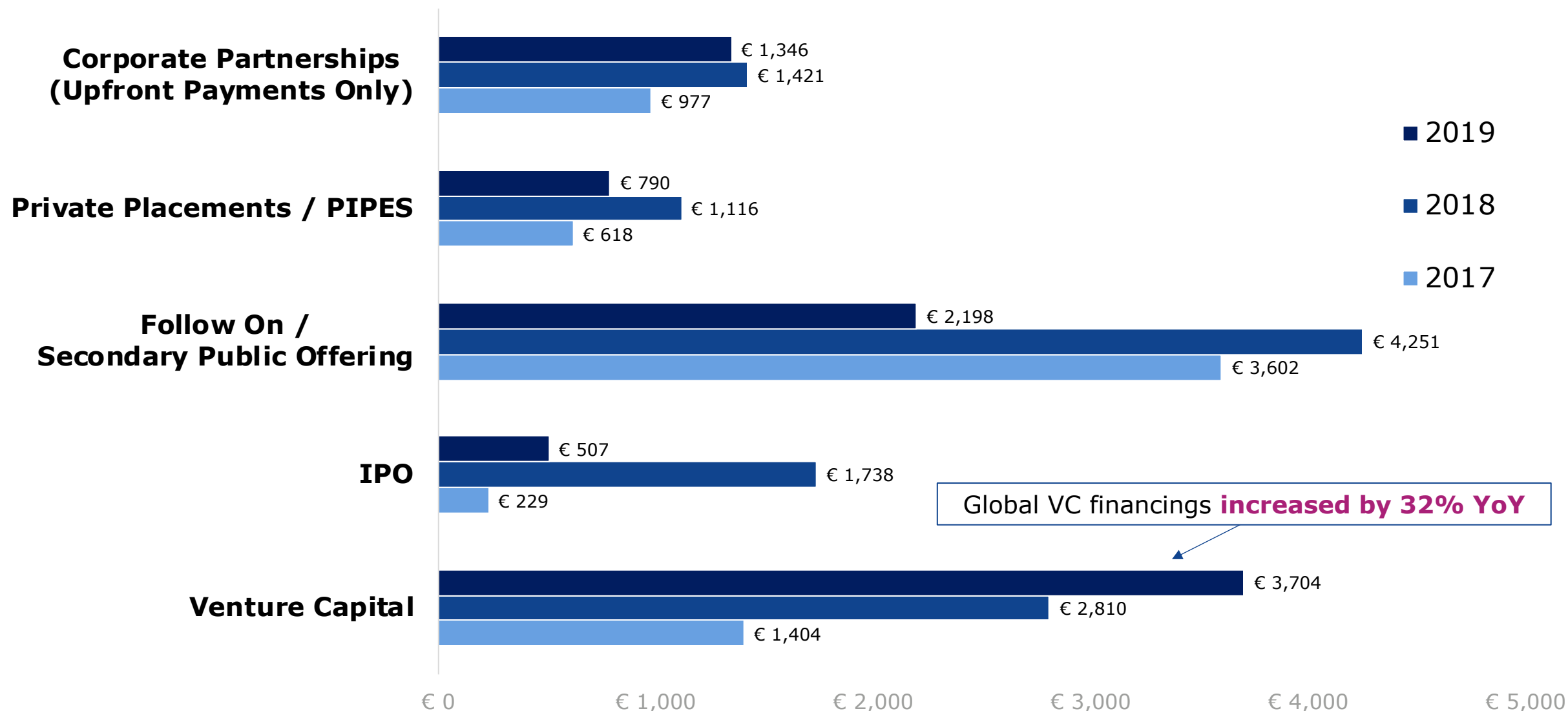
***2019 surpassed 2015 in total global financings, making it the second highest year for financings ever***

# Total Financings by European-Based Companies



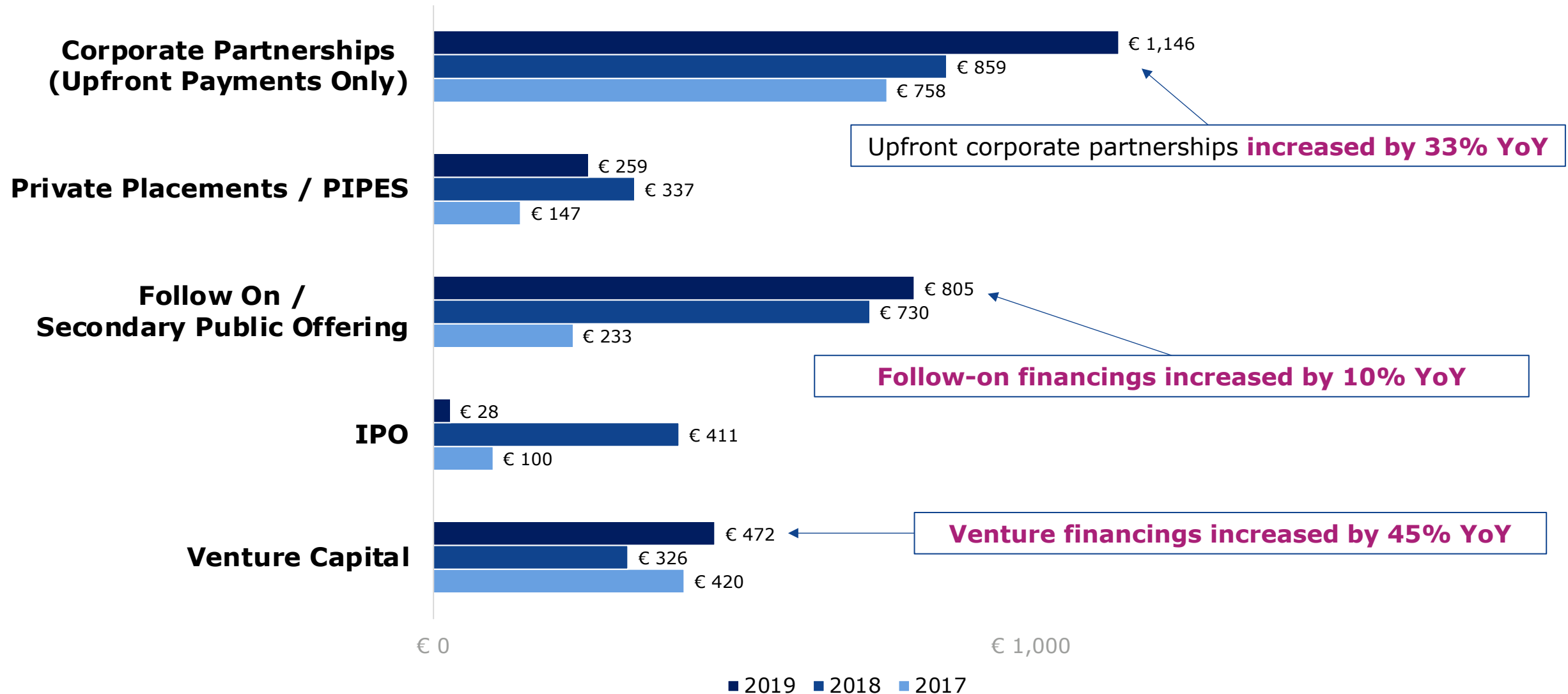
***2019 was the best year on record for financings by European-headquartered companies (up 1% YoY)***

# Global Financings by Type & Year



# Global Financings by Type & Year

## For European HQ'd Companies



# Select Corporate Partnerships & Financings 2019

## *For European HQ'd Companies*

### Corporate Partnerships: (Upfront Payments)

- Genentech/Roche signs **€270M (\$300M)** upfront agreement with Adaptive Biotechnologies – Jan 4
- Vertex signs **€158M (\$175M)** upfront agreement with CRISPR Tx – June 6
- Mesoblast signs **€135M (\$150M)** upfront agreement with Grünenthal – Sep 10
- Turnstone Biologics signs **€108M (\$120M)** upfront agreement with Takeda – Dec 19
- Neurocrine Bio and Voyager Tx sign **€104M (\$115M)** upfront agreement – Jan 29
- Janssen signs **€90M (\$100M)** upfront agreement with MeiraGTx – Jan 31
- Astellas Pharma signs **€72M (\$80M)** agreement with Frequency Therapeutics – July 17
- Voyager signs **€59M (\$65M)** upfront agreement with AbbVie – Feb 21

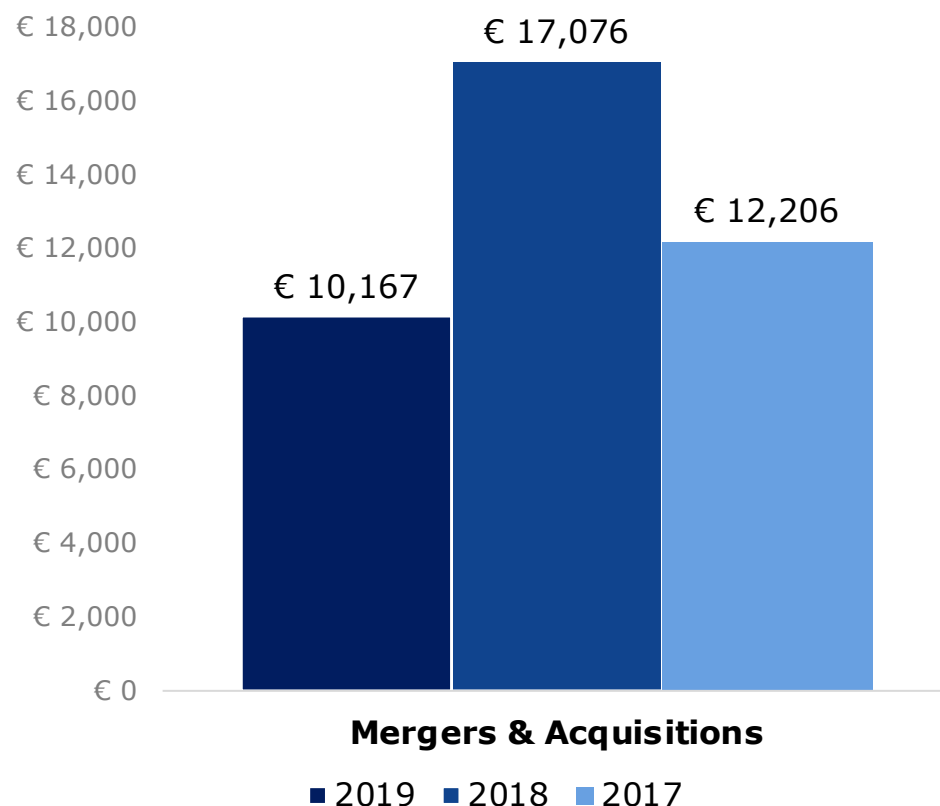
### Venture & Other Financings:

- Achilles Tx raises **€109M (\$121M)** in Series B – Sep 3
- Avita Medical raises **€74M (\$82M)** in private placement – Nov 13
- Oxford Biomedica raises **€61M (\$68M)** in private placement – May 28
- Unicyte raises **€60M (\$66M)** in Series A – Sep 5
- Gyroscope raises **€55M (\$61M)** in Series B – Sep 3

### Public Offerings: (IPOs & Follow-Ons)

- CRISPR Tx raises **€247M (\$274M)** in follow-on offering – Nov 19
- uniQure raises **€203M (\$225M)** in follow-on offering – Sep 4
- Orchard Tx raises **€115M (\$128M)** in follow-on offering – June 3
- Autolus raises **€105M (\$116M)** in follow-on offering – April 15

# M&A Activity Reflects Growing Interest in Cell & Gene Therapy



## Large and mid-cap pharma/bio acquisitions in the sector:

- Astellas acquires Audentes Tx for €2.7B (\$3B)\*
- Roche acquires Spark Tx for €4.3B (\$4.8B)
- Vertex acquires Semma for €856M (\$950M)
- Biogen acquires Nightstar Tx for €791M (\$877M)
- Bayer acquires remaining stake in BlueRock Tx for €216M (\$240M)

*\*Not included in 2019 figure; deal closed Q1 2020*

# Looking Forward: 2020+

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# The Outlook for 2020



## Clinical Data Readouts

*Numerous high-profile data readouts expected in 2020*



## Hospital Exemption

*Additional focus on safety & efficacy for point-of-care administration*



## Product Approvals

*Several anticipated product approvals; gene therapies likely to double within 1-2 years*



## Stem Cell Clinics

*Additional enforcement actions to be taken against 'rogue' stem cell clinics*



## Sector Financing

*Strong demand for financing; IPO market constrained by US elections; indications generally strong*



## Drug Pricing

*Moderate solution with increased emphasis on value in the RM sector*



## Gene Therapy Advances

*Continued improvements in gene therapy delivery & manufacturing*



## Regulatory Environment










*Continued support for the sector, with additional RMAT / PRIME designations expected*

- Clinical Trial Regulation implementation
- GMO requirements for clinical trials with gene therapies
- Medical Device and In vitro Regulations implementations
- Review of the Blood, Cells & Tissues Directives
- Hospital Exemption

***Potential opportunities to increase Europe's competitiveness on ATMP development***

# Patient Access to Regenerative Medicines Is Increasing Rapidly

## Positive reimbursement decisions for select regenerative medicine products

	 France	 Germany	 UK	 Italy	 Spain	 US	 Canada	 Australia	 Japan
<b>Imlygic</b> <i>Melanoma</i>			✓	✓		✓			
<b>Holoclax</b> <i>Corneal Injury</i>			✓	✓					
<b>Strimvelis</b> <i>ADA-SCID</i>			✓	✓					
<b>Alofisel</b> <i>Crohn's</i>		✓			✓				
<b>Kymriah</b> <i>Blood cancers</i>	✓	✓	✓	✓	✓	✓	✓	✓	✓
<b>Yescarta</b> <i>Blood cancers</i>	✓	✓	✓	✓	✓	✓	✓		
<b>Luxturna</b> <i>IRD</i>		✓	✓			✓			
<b>Zolgensma</b> <i>SMA</i>						✓			

- = Product approved, but not currently reimbursed
- = Positive reimbursement
- = Product not currently approved

# Getting Ready for ATMPs in Europe



- Brings together the views of a number of European policy makers and experts
- Recommendations:
  1. Better adapt HTA frameworks to ATMPs
  2. Favor wide application of conditional reimbursement schemes
  3. Develop pan-European initiatives (RWE, early dialogues, cross-border treatment)
  4. Favor wider application of innovative access and funding arrangements

Report released on July 19, 2019 and available at <https://alliancerm.org/publications-presentations/>  
See also [ARM recommendations on cross-border and regional access to ATMPs in Europe](#) released on 27 Jan 2020

## In Summary

- 2019 a year of significant growth in the regenerative medicine sector; we enter 2020 poised for continued expansion
- Many patients are already benefitting from regenerative medicines, and the clinical results are dramatic
- The pipeline is robust, with several next-gen technologies entering the clinic and an increase in clinical trials for indications with large patient populations
- Considerable effort and progress in addressing various manufacturing challenges
- While financing dipped in 2019 vs. 2018, financing remains strong across venture capital and partnerships, with M&A activity showcasing large and middle cap pharma's interest in the cell & gene therapy space

# Thank You!

Visit [www.alliancerm.org](http://www.alliancerm.org) to access additional resources, including:

- Slides from this and other ARM presentations
- Quarterly sector data reports
- Upcoming near-term clinical trial milestones & data readouts
- Our weekly sector newsletter, a robust round-up of business, clinical, scientific, and policy news in the sector
- Commentary from experts in the field