State of the Industry

Cell & Gene Therapy Sector Update

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18 October 2018

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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State of the Industry Briefing

- **Global Sector Overview:** 2018
- **Clinical Progress:** YTD 2018
- **Anticipated Clinical Data Events:** 2018+
- **Sector Financings:** YTD 2018
- **Reimbursement Environment**

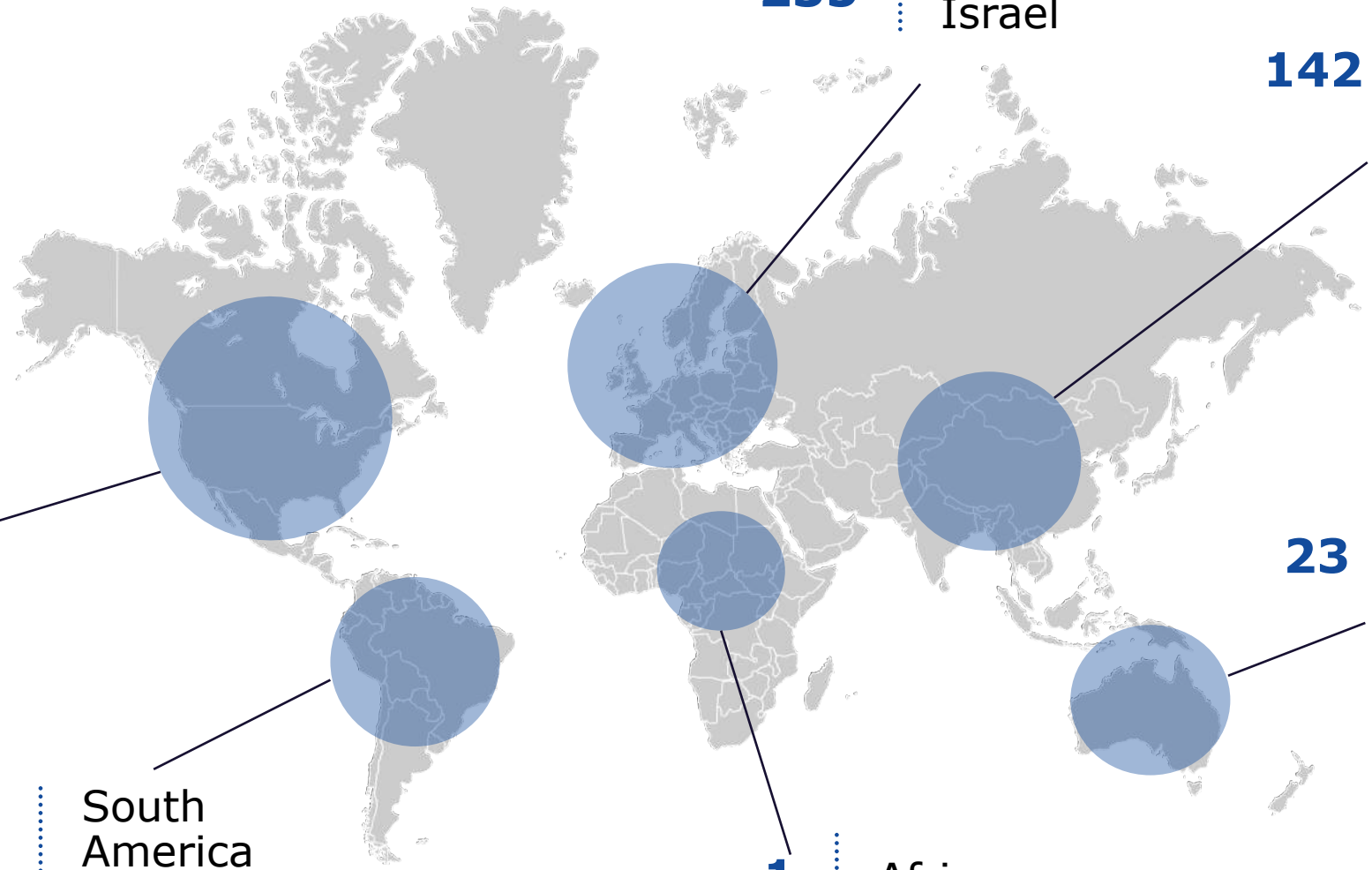
A Quick Note -

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

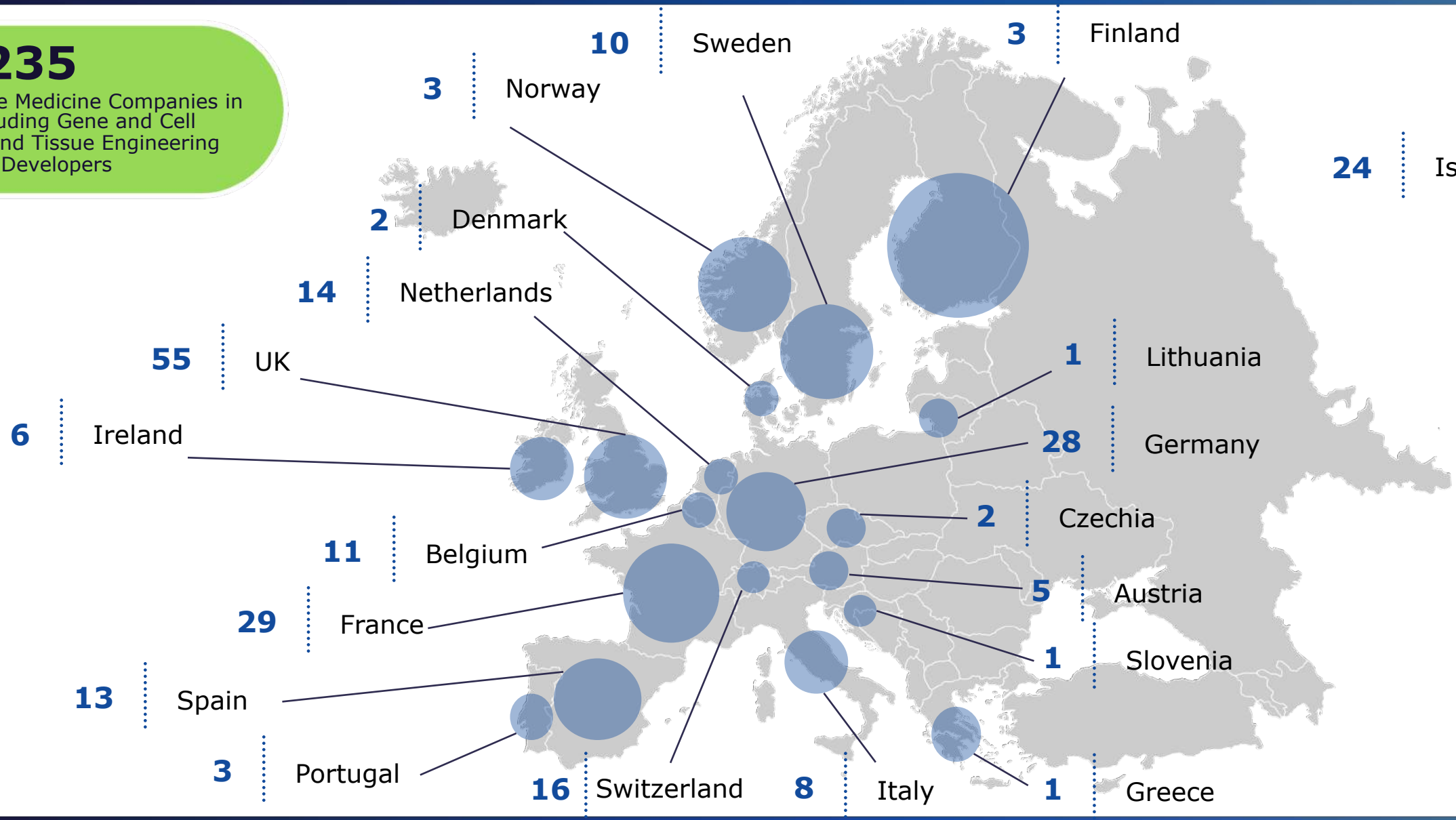
1 Africa

Source data provided by: informa

European Sector Overview

235

Regenerative Medicine Companies in Europe, including Gene and Cell Therapies, and Tissue Engineering Therapeutic Developers



Major Therapeutic Platforms & Enabling Technologies

- **Advanced cells:** Modified T-cells; hematopoietic stem cells; iPSCs; mesenchymal stem cells; adult progenitor cells (neural, liver, cardiac); etc.
- **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.
- **Novel and synthetic gene delivery vehicles:** Viral vectors: retroviruses, adenoviruses, herpes simplex, vaccinia, and adeno-associated virus (AAV); Non-viral vectors: nanoparticles and nanospheres
- **Genome 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.
- **Next-gen expression constructs:** novel capsids; innovative regulatory elements, including synthetic promoters that enable specificity, strength, and improve capacity; inducible elements to regulate gene expression temporally or in response to external stimuli: molecular kill switches to improve safety; etc.

Recent Product Approvals

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Approvals YTD 2018:

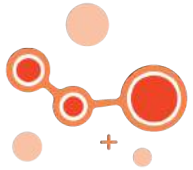
- Spark Therapeutics' **LUXTURNA** gene therapy for biallelic RPE65-mediated inherited retinal disease received positive CHMP opinion – September 21
- Avita Medical's **RECELL** system for serious burns received FDA approval for the treatment of severe burns – September 20
- Gilead / Kite Pharma's **Yescarta** cell therapy received approval from the European Commission for the treatment of DLBCL– August 27; approval from the European Commission to treat adult patients with r/r DLBCL and PMBCL – August 27
- Novartis's **Kymriah** received FDA approval for a second indication: treatment of adult patients with r/r large B-cell lymphoma – May 1; approval from the European Commission for adult patients with r/r DLBCL and patients under the age of 25 with ALL – August 27
- TiGenix's (now Takeda's) **Alofisel** (previously Cx601) allogeneic stem cell therapy for treatment of perianal fistulas in Crohn's disease patients received central marketing authorization from the European Commission – March 23

Total Clinical Trials by Phase - End Q3 2018

Phase I

330

7.5%
increase YoY



Phase II

580

6%
increase YoY

Phase III

93

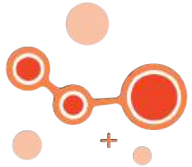
18%
increase YoY

Source data provided by: informa

Total Clinical Trials by Technology Type – End Q3 2018

Gene Therapy

Total: 351
Phase I: 114
Phase II: 204
Phase III: 33

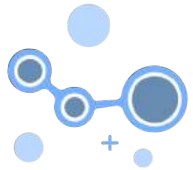


Gene-Modified Cell Therapy

Total: 328
Phase I: 145
Phase II: 168
Phase III: 15

Cell Therapy

Total: 283
Phase I: 61
Phase II: 189
Phase III: 33

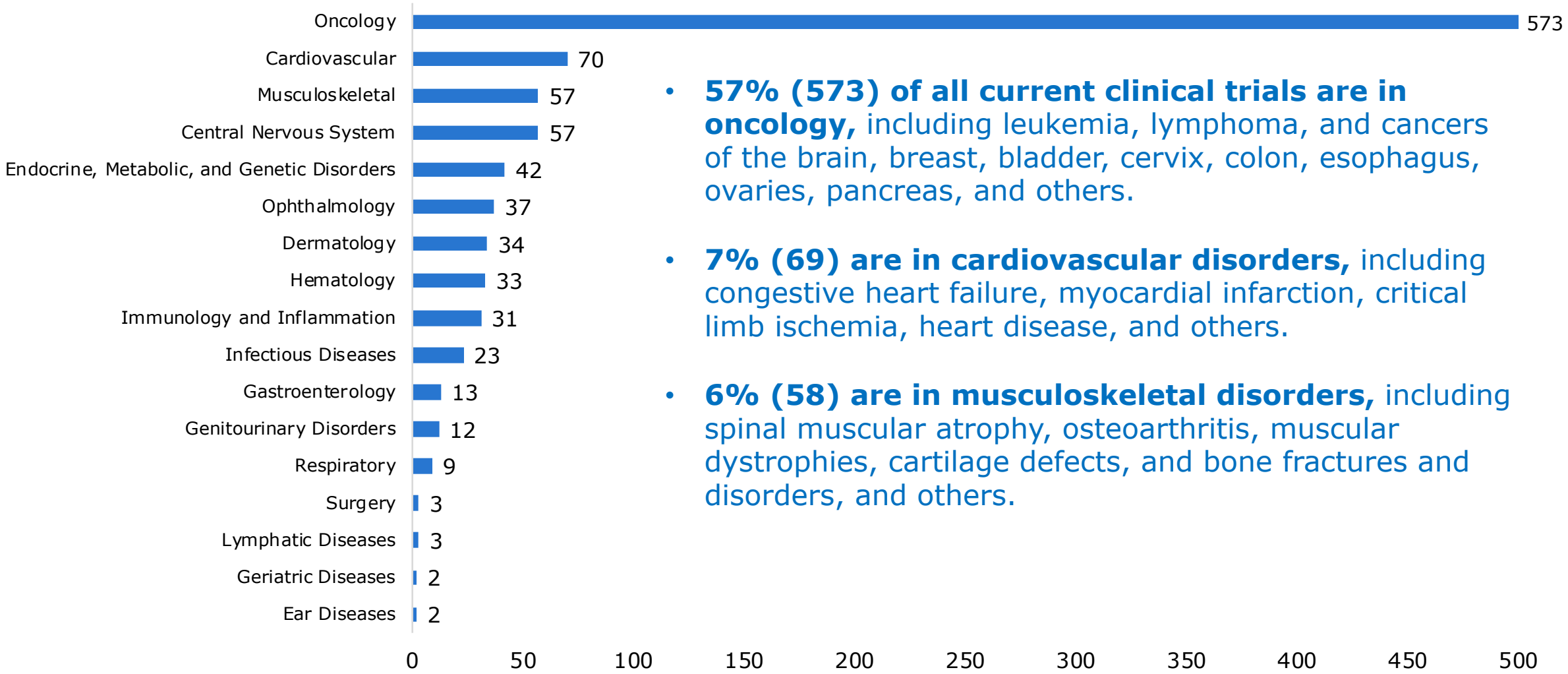


Tissue Engineering

Total: 41
Phase I: 10
Phase II: 19
Phase III: 12

Source data provided by: informa

Clinical Trials by Therapeutic Category



- **57% (573) of all current clinical trials are in oncology,** including leukemia, lymphoma, and cancers of the brain, breast, bladder, cervix, colon, esophagus, ovaries, pancreas, and others.
- **7% (69) are in cardiovascular disorders,** including congestive heart failure, myocardial infarction, critical limb ischemia, heart disease, and others.
- **6% (58) are in musculoskeletal disorders,** including spinal muscular atrophy, osteoarthritis, muscular dystrophies, cartilage defects, and bone fractures and disorders, and others.

Source data provided by: informa

Select Anticipated Late-Stage Data Events: 2018+

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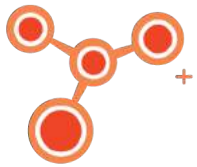
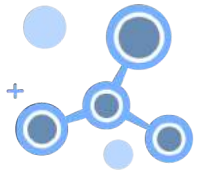
Company	Product	Therapeutic Modality	Indication	Clinical Stage	Expected Reporting Date
Kiadis	ATIR101	Allodepleted T-Cell Immunotherapy	AML or ALL	Conditional EU approval	On track to receive CHMP opinion Q4 2018; launch 2019
bluebird bio	Lentiglobin	Gene therapy	Transfusion dependent beta-thalassemia	MAA filing	EMA accepted MAA; will be evaluated under accelerated assessment, decision expected 2019
Orchard Therapeutics	OTL-200	Gene therapy	metachromatic leukodystrophy	MAA filing	To file MAA 2020, followed by a BLA with the FDA
Enzyvant Tx	RVT-802	Tissue-based therapy	Complete DiGeorge Syndrome	BLA submission	Initiation of rolling BLA submission in July 2018; BLA expected to be completed in 2018
Juno/Celgene	Liso-cel (formerly JCAR017)	CAR-T cell therapy	NHL	BLA submission	2H 2018
PTC Therapeutics	GT-AADC	Gene therapy	AADC Deficiency	BLA submission	Expects to submit BLA in 2019
bluebird bio / Celgene	bb21217	CAR-T	third line multiple myeloma	Ph III	Study to be initiated by Celgene in 2H 2018
bluebird bio	Lentiglobin	Gene therapy	Transfusion dependent beta-thalassemia & beta-0/beta-0 genotypes	Ph III – Northstar-3 (HGB-212)	End-year 2018
bluebird bio	Lenti-D	Gene therapy	Cerebral Adrenoleukodystrophy	Ph III – Starbeam 102	End-year 2018
Abeona	EB-101	Gene therapy	Epidermolysis Bullosa	Ph III	Trial commences 2018
Athersys	MultiStem	Cell therapy	Ischemic Stroke	Ph III (under SPA)	Initiating 2018
AveXis	AVXS-101	Gene Therapy	Pediatric SMA Types 1, 2, and 3	Ph III	Expected to initiate in late Q4 2018 or early 2019.
BioMarin	Valoctocogene roxaparvovec	Gene therapy	Hemophilia A	Ph III	Increase in enrollment to 130 participants anticipated by 1Q 2019

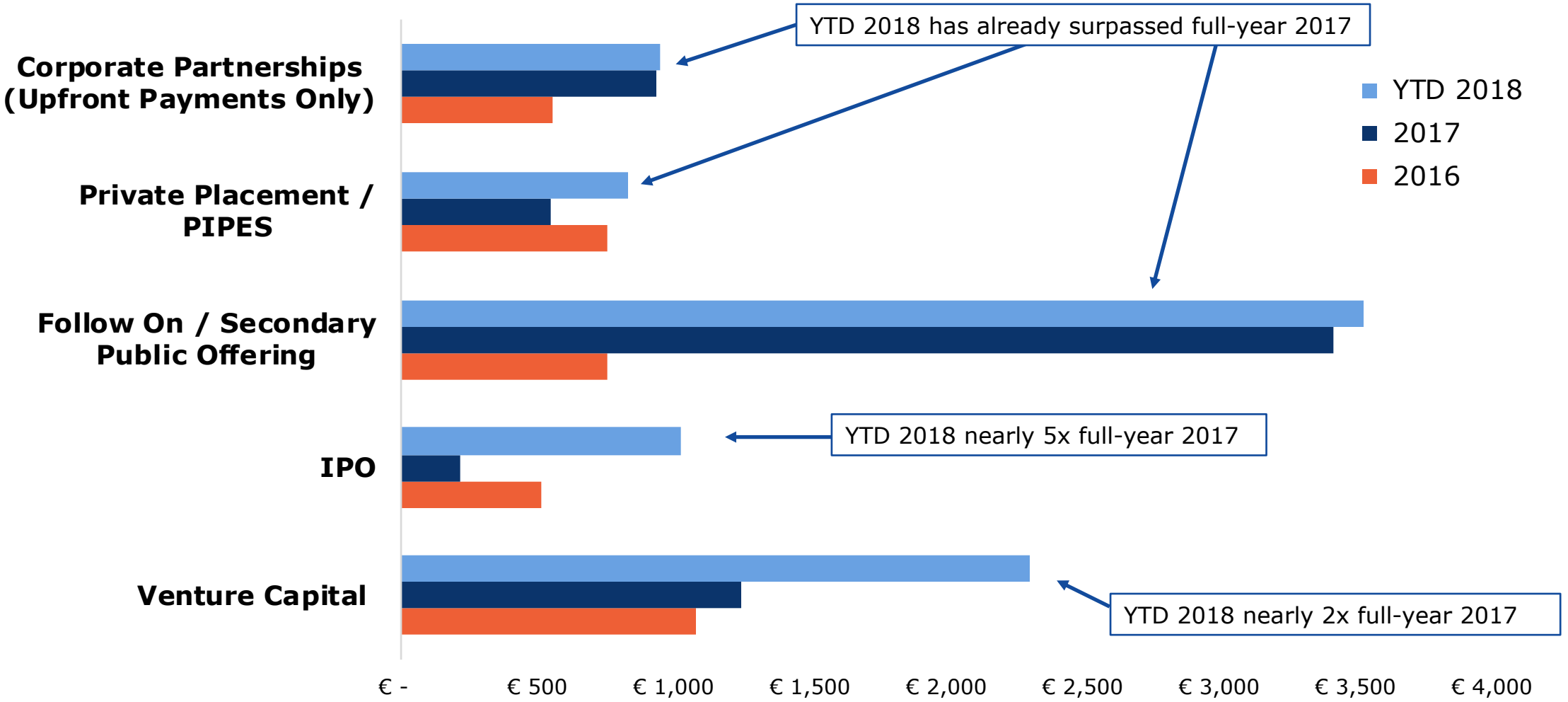
Total Global Financings: Q3 2018

	**€2.4B**	**Total Global Financings Q3 2018**	**59%** increase from Q3 2017	**40%** increase YOY (€9.2B YTD 2018)
	**€1.8B**	**Gene-Based Therapies Q3 2018 Financings**	**35%** increase from Q3 2017	**34%** increase YOY (€6.7B YTD 2018)
	**€1.6B**	**Cell Therapy Q3 2018 Financings**	**73%** increase from Q3 2017	**32%** increase YOY (€5.2B YTD 2018)
	**€1.3M**	**Tissue Engineering Q3 2018 Financings**	**91%** decrease from Q3 2017	**213%** increase YOY (€678.3M YTD 2018)

Source data provided by: informa

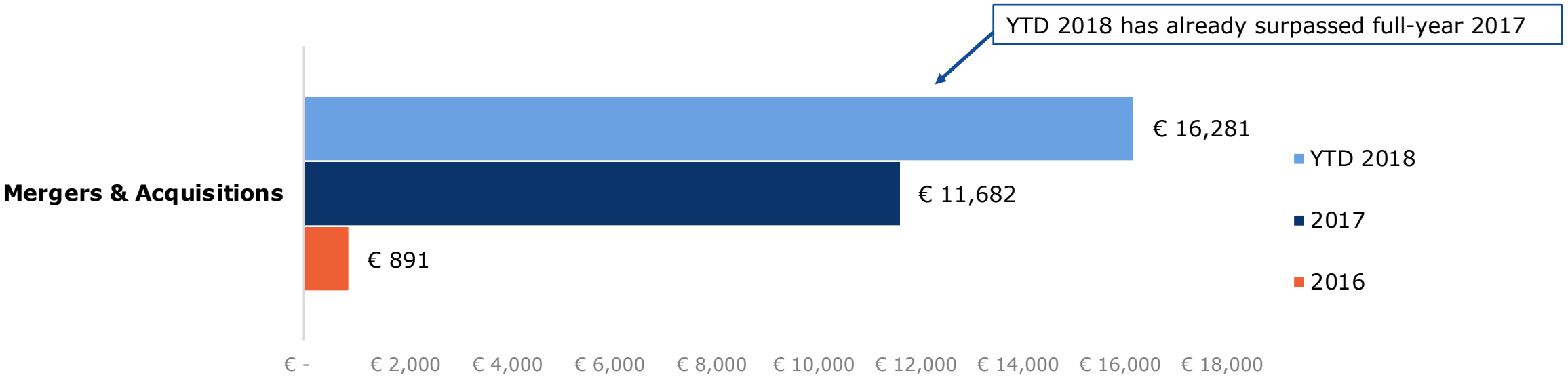
**both Gene-Based Therapies & Cell Therapy categories include financings from companies active in developing gene-modified cell therapies*

Total Financings by Type, by Year



Source data provided by: informa

Total M&A Transactions Values, By Year



Source data provided by: informa

Select Corporate Partnerships & Public Financings: YTD 2018

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Corporate Partnerships: (Upfront Payments)

- Genmab signs €47M upfront agreement with Immatics – July 12
- Mesoblast signs €35M upfront agreement with Tasly – July 17
- bluebird bio signs €26M upfront agreement with Gritstone Oncology – August 23
- Allergan exercises €13M upfront option agreement with Editas Medicine – August 6
- CRISPR Therapeutics signs €13M upfront agreement with ViaCyte – September 17

Private Placements & Venture Financings:

- Orchard Therapeutics €130M Series C – August 13
- Allogene €104M Venture Financing – September 6
- bluebird bio €86M Private Placement – August 6
- 4D Molecular Tx €78M Venture Financing – September 5
- SQZ Biotechnologies €62M Venture Financing – August 8
- Ambys Medicines €52M Series A – August 8
- Akouos €43M Series A – August 7
- AgeX €37M Private Placement – September 4
- SCM Lifescience €30M Series C – September 7
- Recombinetics €29M Private Placement – August 21
- Lacerta Tx €26M Private Placement – August 8

Public Offerings: (IPOs & Follow-On Financings)

- bluebird bio €546M follow-on financing – July 27
- Rubius Tx €239M initial public offering – July 23
- REGENXBIO €174M follow-on financing – August 14
- CRISPR Tx €173M follow-on financing – September 19
- Fate Tx €124M follow-on financing – September 25
- Adaptimmune €86M follow-on financing – September 7

M&A Activity: (Upfront Payments)

- Takeda acquires TiGenix for €540M upfront – July 31
- PTC Tx acquires Agilis for €173M upfront – August 23
- Astellas acquires Quethera for €93M upfront – August 10

Market Access Landscape: EU & U.S.

Key:
- HTA Negative opinion
- HTA positive opinion
- HTA positive opinion with limitations

✓ Reimbursed
✓ Not reimbursed
X Withdrawn from market

		France (TC/CEESP)	Germany (IQWIG/ G-BA)	UK (NICE/SMC)	Italy (AIFA/ regional)	Spain (national/ regional)	Netherlands (ZIN/CVZ)	Denmark (MTN)	U.S. (CMS)
Gene Therapies	Glybera X	✓	Non-quantifiable added benefit ✓	-	-	-	-	-	-
	Imlygic	-	No added benefit but reimbursed ✓	PAS ✓	Authorized, hospital only, Cnn	-	Conditional reimbursement ✓	-	Approved by FDA Oct 2015 ✓
	Strimvelis	-	- ✓	✓	Hospital only, innovative status, annuity payment by results ✓	-	-	-	-
	Kymriah	-	-	Contract with NHS ✓	-	-	-	-	Approved by FDA Aug 2018 ✓
	Yescarta	-	-	Negative NICE Draft Guidance	-	-	-	-	Approved by FDA Aug 2018 ✓
	Luxturna	-	-	-	-	-	-	-	Approved by FDA Dec 2017 ✓
Cell Therapies	Provenge X	-	Non-quantifiable added benefit ✓		-	-	-	-	Approved by FDA 2010 ✓
	Zalmoxis	-	Non-quantifiable added benefit ✓	-	Hospital only, flat cost per patient ✓	-	-	-	-
	Alofisel	-	Non-quantifiable added benefit ✓	Negative NICE Draft Guidance	-	-	-	-	-
Tissue Therapies	Chondrocelect X		Not eligible for EBA	Negative NICE Guidance	-	National reimbursement ✓	CVZ negative advice but reimbursed ✓	Hospital use, no HTA ✓	-
	MACI X	-	Not eligible for EBA	Negative NICE Guidance	-	-	-	-	Approved by FDA Dec 2016 ✓
	Holoclar	✓	Not eligible for EBA	PAS ✓	Hospital only payment by results ✓	-	-	Hospital use, no HTA ✓	-

As of September 2018; Adapted from Creativ-Ceutical's EU market access landscape assessment for ARM

Landscape Summary

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Supportive policy environment:

- U.S., EU, and globally

Strong scientific data:

- Potential for positive, widespread patient impact
- Significant near-term late-stage anticipated clinical milestones

Sustained investor, partnering interest:

- Substantial year-over-year increases across financing types
- Significant increase in IPO activity
- Strong M&A activity; additional activity anticipated

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 challenges

Thank You!

This presentation & more information can be found via:

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

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