Quarterly Data Report

Alliance *for*
Regenerative Medicine

The Alliance for Regenerative Medicine (ARM) is the preeminent global advocate for regenerative and advanced therapies. ARM fosters research, development, investment and commercialization of transformational treatments and cures for patients worldwide.

By leveraging the expertise of its membership, ARM empowers multiple stakeholders to promote legislative, regulatory and public understanding of, and support for, this expanding field.

www.alliancerm.org

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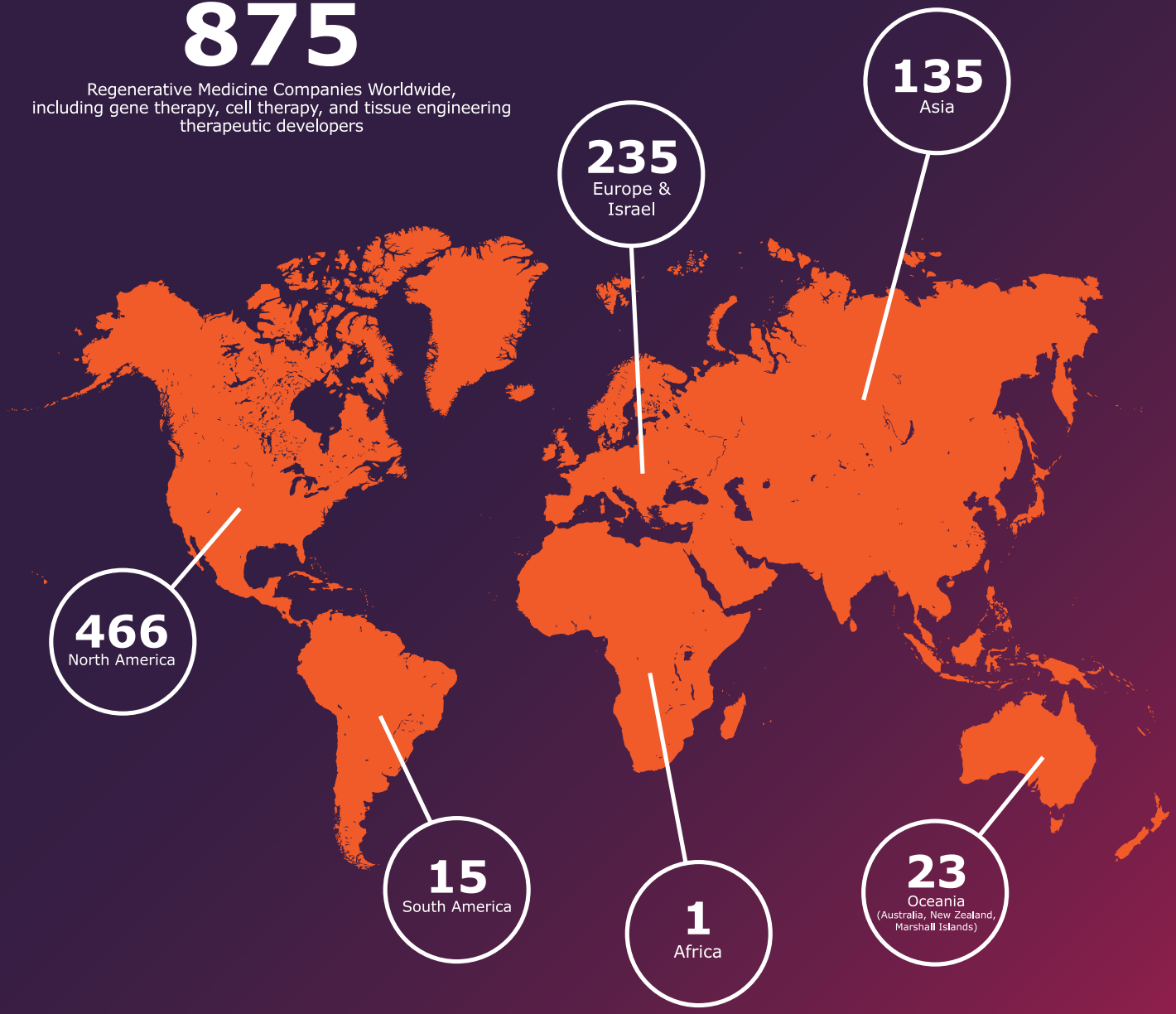
Global Landscape

875

Regenerative Medicine Companies Worldwide, including gene therapy, cell therapy, and tissue engineering therapeutic developers



Industry Overview

Q2 Summary Overview

One of the top stories of the second quarter of 2018 has to be the surge in the number of IPOs filed by regenerative medicine companies. The total number of filings in the first half of 2018 has jumped from previous years, exhibiting investors' continuing confidence in the advanced therapies sector. Companies that filed in Q2 include: MeiraGTX, Autolus, AVROBIO, and Magenta. These companies join Homology Medicines, Genprex, Unum Therapeutics, and Solid Biosciences in IPO filings for 1H 2018.

The second quarter also began with the high-priced acquisition of AveXis for $8.7 billion as Novartis builds its gene therapy portfolio. GI Partners agreed to purchase the Cord Blood Registry, a cord blood stem cell collection and storage company, from AMAG Pharmaceuticals, Inc. for $530 million in an all-cash transaction that is expected to close in the third quarter.

Rounds of financing were also successful and plentiful. In Series A rounds, Tmunity raised an additional $35 million; Allogene launched, raising $300 million; and Beam Therapeutics launched and raised $87 million. Freeline and Precision Bio raised $116.6 million and $110 million, respectively, in Series B rounds. Biocytogen raised $65 million and Decibel landed $55 million in Series C rounds.

Other financing rounds were equally valuable. Sangamo closed a follow-on public offering that raised $230 million, while Cellectis announced a closing of $163.7 million in a follow-on public offering. uniQure N.V. raised $147.49 million, Vericel raised approximately $74.8 million, and MediGene AG raised $37.91 million. Celyad also announced a closing of a global offering netting approximately $54.5 million in private placement of shares. TapImmune announced their intent to raise $70 million from private placement of shares, while Intrexon expects to raise $100 million in a public offering.

In partnerships this quarter, Siglion received an upfront payment of $63 million from Eli Lilly to develop engineered iPSCs to become insulin-producing beta cells. Milestones could go as high as $410 million. bluebird bio expanded its partnership with Medigene for two additional TCR targets worth $250 million each in a licensing deal could raise a potential $1.5 billion for Medigene and tiered royalty payments. Editas earmarked $125 million to the Broad Institute for first refusal on genome editing inventions developed in this sponsored research agreement. Humacyte and Fresenius Medical Care announced a global strategic partnership supported by a $150 million equity investment.

And finally, there were four new RMAT designations granted this quarter: Nightstar Therapeutics for a gene therapy to treat choroideremia; Caladrius Biosciences for the CD34+ cell therapy targeting refractory angina; Voyager Therapeutics's gene therapy for Parkinson's disease; and Abeona Therapeutics's second RMAT, this one for the company's ABO-102 gene therapy to treat MPS IIIA.

This sector continues its clinical and commercial uptick, as more investors and other stakeholders take notice. The second half of the year likely holds additional accomplishments for the field.

–Patricia Reilly
Vice President, Intelligence Alliances and Unification
Pharma Intelligence | Informa

Global Financings

Total Q2 2018 Global Financings

TOTAL GLOBAL FINANCINGS

$4.1 Billion raised in Q2 2018
164% increase from Q2 2017
$7.9 Billion raised YTD 2018
79% increase year-over-year

GENE & GENE-MODIFIED CELL THERAPY

$2.7 Billion raised in Q2 2018
124% increase from Q2 2017
$5.8 Billion raised YTD 2018
133% increase year-over-year

CELL THERAPY

$2.2 Billion raised in Q2 2018
416% increase from Q2 2017
$4.2 Billion raised YTD 2018
83% increase year-over-year

TISSUE ENGINEERING

$421 Million raised in Q2 2018
526% increase from Q2 2017
$784 Million raised YTD 2018
25% increase year-over-year

*Total amount raised represents sector-wide figures; please note that some companies utilize technology from more than one technology group. As a result, the total financings amount does not equal the sum of the raises of the individual technology groups.

** Figures do not include M&A transaction totals.

Examples of Key Financings: Q2 2018

Public offerings:

- Sangamo Therapeutics raises $230 million in follow-on financing – April 30
- Cellectis raises $190.5 million in follow-on financing – April 10
- Autolus raises $172.5 million in initial public offering – June 26
- Homology Medicines raises $165.6 million in initial public offering – April 3
- uniQure raises $147.5 million in follow-on financing – May 7
- AxoGen raises $141.5 million in follow-on financing – May 14
- AVROBIO raises $114.7 million in initial public offering – June 25
- Magenta Therapeutics raises $100 million in initial public offering – June 25

Corporate partnerships and other financings:

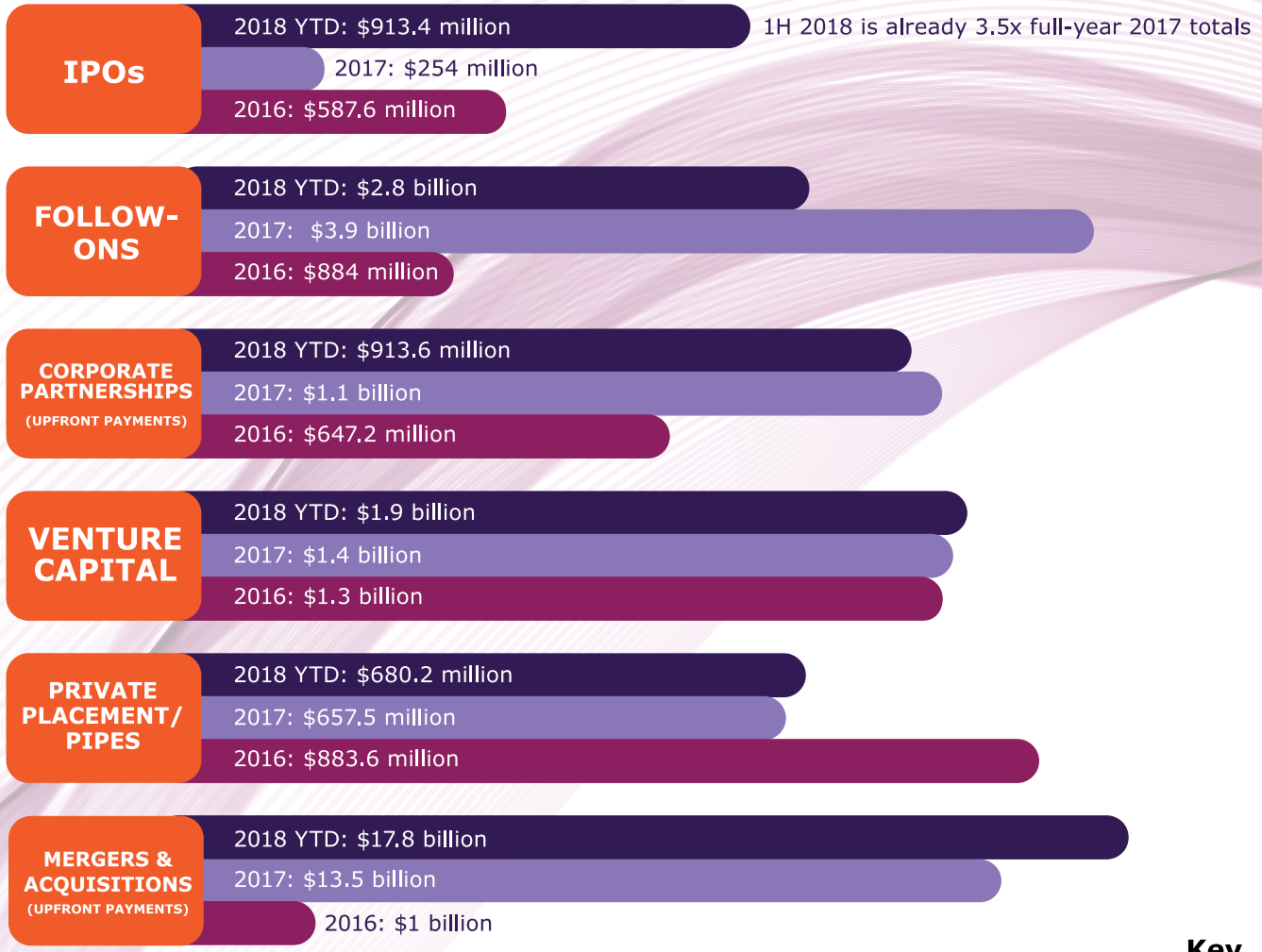
- Allogene secures $300 million in venture financing – April 3
- Humacyte receives $150 million in private placement – June 11
- Freeline Therapeutics secures $116.6 million in venture financing for Series B funding – June 19
- Precision Biosciences raises $110 million in private equity during Series B financing – June 26
- Spark Therapeutics signs $110 million upfront agreement with Jazz Pharmaceuticals – April 30
- REGENXBIO receives $100 million accelerated license payment from AveXis – June 11

M&A Activity:

- Novartis acquires AveXis for $8.7 billion – May 15

Global Financings

Total Global Financings by Type, by Year



Commentary: RMAT Designation

RMAT Designation – Its Impact on the Regenerative Medicine Sector & How it Compares to Other Accelerated Approval Programs

In June 2018, ARM and Informa co-hosted a webinar on the Regenerative Medicine Advanced Therapy (RMAT) Designation. Launched in 2017, the RMAT designation optimizes the FDA's approval pathway for qualifying regenerative medicine and advanced therapy products, fostering development of these therapies while maintaining the FDA's high safety and efficacy standards for approval. To date, the FDA has granted 20 RMAT designations, the majority of which focus on rare diseases.

Michael Werner, ARM's Co-founder and Senior Policy Counsel, joined Tim Miller, President & Chief Scientific Officer of Abeona Therapeutics; Gil Van Bokkelen, CEO of Athersys; Kevin Healy, Global Regulatory Lead at Roivant Sciences, representing Enzyvant Therapeutics; and Amanda Micklus and Patty Reilly of Informa to compare the RMAT designation to other accelerated approval designations, discuss the benefits of an RMAT designation, and give the companies' perspectives on obtaining the designation.

The webinar recording and slides are available on ARM's website: **www.alliancerm.org.**

How RMAT Designation Compares to Breakthrough Therapy Designation

	Breakthrough Therapy Designation	RMAT Designation
Use of preliminary clinical evidence to support designation	✓	✓
Use of preliminary non-clinical evidence to support filing	X	X
Frequent interactions with FDA for discussions e.g. study design, extent of safety data required to support approval, dose-response concerns, and use of biomarkers	✓	✓
Eligible for priority review	✓	✓
Eligible for accelerated approval	✓	✓
Restricted to regenerative medicines	X	✓
Show substantial improvement on clinically significant endpoint(s) over available therapy	✓	X
Early interactions with FDA to discuss and determine potential surrogate or intermediate endpoints in support of accelerated approval	X	✓
Regulatory interactions with FDA should be more focused around manufacturing issues	X	✓

Chart courtesy of Amanda Micklus, Informa

Commentary: RMAT Designation

Highlighted Commentary from the Webinar:

Michael Werner
Co-founder & Senior Policy Counsel,
Alliance for Regenerative Medicine

"[RMAT] really accomplishes all the goals that we had laid out at the beginning of [ARM's] thought process. It protects patients by maintaining the high standards of safety and efficacy, it helps product developers with regulatory clarity and ways that you can access expedited approval, and it brings [the United States] up to par with, or arguably ahead of, our economic competitors. I think the fact that there's so much demand for the designation, and the FDA's interest in promoting the designation, speaks volumes."

–Michael Werner

Kevin Healy
Global Regulatory Lead,
Roivant Sciences, Inc.
Representing Enzyvant Therapeutics

"We've had great interactions with the FDA since the granting of the RMAT designation and encourage sponsors to take advantage of that. Ultimately, you're responsible for driving your development program forward in the most efficient way possible, so you always keep that in mind."

–Kevin Healy

Gil Van Bokkelen
Chief Executive Officer,
Athersys

"I strongly encourage those that are involved in the regenerative medicine and advanced therapies space to focus on RMAT. I think it's a regulatory designation that has specifically been created for these types of therapies and I think it provides substantial benefits in terms of the interactions with the FDA and other elements."

"I think from a global perspective, it's important for everyone to recognize and remember that the FDA has a very important and, frankly, a sacred responsibility to provide oversight that is designed to help protect and ensure the well-being of patients. The FDA consists of people just like the rest of us. They're deeply committed to seeing safer and more effective medicines developed. They want to see us succeed in the development of these innovative medicines. There are a number of different reasons for this, but one obvious one is just like the rest of us, the FDA has sick family members or loved ones and they want to see the boundaries of medicine advance. The RMAT designation has been designed and implemented to help us and to promote that innovation."

–Gil Van Bokkelen

Tim Miller
President & Chief Scientific Officer,
Abeona Therapeutics

"As you think about trying to apply for these designations, you really want to try to put yourselves in [the FDA's] shoes. You know, do you believe the clinical data? Is it really a superior product? Is it going to be transformative for patients' lives if this were to be approved? And you should think forward on your approach because that's how they're looking at this. You want to be able to provide a clinical data set that's compelling. […] As the space moves forward, particularly in the gene therapy space, I think you'll see a number of additional RMAT designations granted because there's been such positive momentum."

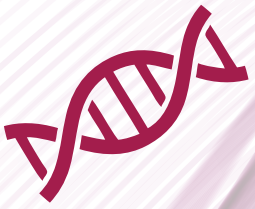
–Tim Miller

Clinical Trials

977
Clinical trials underway worldwide by end of Q2 2018

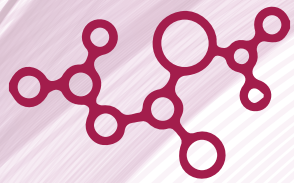
Ph. I: 324
Ph. II: 560
Ph. III: 93

Number of Clinical Trials Utilizing Specific RM/AT Technology: Q2 2018



Gene Therapy

Total: 317
Ph. I: 109
Ph. II: 174
Ph. III: 34



Gene-Modified Cell Therapy

Total: 314
Ph. I: 134
Ph. II: 166
Ph. III: 14

Cell Therapy

Total: 322
Ph. I: 76
Ph. II: 208
Ph. III: 38

Tissue Engineering

Total: 24
Ph. I: 5
Ph. II: 12
Ph. III: 7

Clinical Trials by Indication: Q2 2018

- 532 (54%) 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.
- 74 (7.5%) are in cardiovascular disorders, including congestive heart failure, myocardial infarction, critical limb ischemia, heart disease, and others.
- 61 (6%) are in musculoskeletal disorders, including spinal muscular atrophy, osteoarthritis, muscular dystrophies, cartilage defects, and bone fractures and disorders.

Major Milestones & Key Data Events

Select Significant Clinical & Data Events: Q2 2018

Gene Therapy & Genome Editing Programs

- MeiraGTx's AAV-CNGA3 gene therapy for the treatment of achromatopsia caused by mutations in the CNGA3 gene received positive opinion for Orphan Drug Designation in the European Union – June 26
- Voyager Therapeutics's VY-AADC for the treatment of Parkinson's disease received RMAT designation from the FDA – June 21
- Nightstar Therapeutics's NSR-REP1 gene therapy for the treatment of Choroideremia received RMAT designation from the FDA – June 14
- bluebird bio announced data from its ongoing Phase III trial of LentiGlobin gene therapy in patients with transfusion dependent beta thalassemia and non-β0/β0 genotypes
    - Seven of 8 patients were producing ≥ 7.6 g/dL of HbA^{T87Q} and were maintaining total hemoglobin levels of 11.1 – 13.3 g/dL by 6 months.
- REGENXBIO's RGX-111 gene therapy for the treatment of MPS I received Fast Track designation from the FDA – June 12
- GenSight Biologics reported positive additional data from reverse Phase III clinical trial of GS010 for treatment of leber hereditary optic neuropathy (LHON) – June 12
    - Topline results showed that the clinically significant improvement in GS010-treated eyes was matched by an unexpected improvement in the sham-treated eyes.
- Audentes Therapeutics's AT132 for the treatment of X-Linked Myotubular Myopathy received PRIME designation from the EMA – June 5
- Krystal Biotech's KB-103 for the treatment of Dystrophic Epidermolysis Bullosa received Fast Track designation from the FDA – May 24
- bluebird bio's Lenti-D gene therapy for the treatment of adrenoleukodystrophy received Breakthrough Designation from the FDA – May 23
- Myonexus Therapeutics's MYO-101 gene therapy for the treatment of Limb Girdle Muscular Dystrophy Type 2E received Orphan Drug designation and Rare Pediatric Drug designation from the FDA – May 16
- Orchard Therapeutics's OTL-200 for the treatment of Metachromatic Leukodystrophy received Rare Pediatric Drug designation from the FDA – May 3
- REGENXBIO's RGX-121 gene therapy for the treatment of MPS II received Fast Track designation from the FDA – May 2
- MeiraGTx's AAV-RPGR gene therapy for the treatment of X-Linked Retinitis Pigmentosa received Fast Track Designation from the FDA – April 23
- Abeona's ABO-102 gene therapy for the treatment of MPS IIIA received RMAT designation from the FDA – April 23

Major Milestones & Key Data Events

Cell-Based Immuno-Oncology Programs

- Novartis's Kymriah received positive CHMP opinion for the treatment of r/r ALL and r/r DLBCL – June 29
- Kite/Gilead's Yescarta received positive CHMP opinion for the treatment of r/r DLBCL and PMBCL – June 29
- Novartis JULIET trial of Kymriah demonstrated more than one-year durability of responses in adults with relapsed or refractory DLBCL – June 16
    - A complete response was achieved in 40% of patients and 12% achieved a partial response. Patients had a 65% chance of being relapse-free one year after onset of response.

Cell-Based Therapy Programs

- Mesoblast reported key Day 100 survival outcomes of Phase III trial for remestemcel-L in the treatment of Acute Graft versus Host Disease – June 21
    - Top line Day 100 results demonstrated 87% survival rate for Day 28 responders to remestemcel-L treatment, and an overall survival rate of 75%. Mesoblast believes that successful results from the completed Phase 3 trial, together with Day 180 safety, survival and quality of life parameters in these patients, may provide sufficient clinical evidence to file for accelerated approval of remestemcel-L in the U.S.
- Caladrius Biosciences's CD34+ cell therapy for the treatment of Refractory Angina received RMAT designation from the FDA – June 19
- Chiesi's and Holostem's GPLSCD01 cell therapy for Limbal Stem Cell Deficiency (LSCD) received Orphan Drug designation from the FDA – June 12
- Pluristem Therapeutics reported positive top-line results from its multinational Phase II clinical study of PLX-PAD cells in the treatment of Intermittent Claudication, reducing the risk of revascularization and improving patients' mobility – June 12
- Nohla's Dilanubicel (NLA101) stem and progenitor cell product to treat hematopoietic stem cell patients received PRIME designation from the EMA – June 6
- Caladrius Biosciences's CLBS12 for the treatment of Critical Limb Ischemia received SAKIGAKE designation from the Japan Ministry of Health, Labour and Welfare – April 10

Tissue-Engineered Product Programs

- AVITA Medical announced RECELL data from pivotal trial demonstrating statistically significant reduction in donor skin requirements and pain, increased patient satisfaction and improved donor scar outcomes for second-degree burn patients – April 11

Current Regulatory & Legislative Priorities

ARM's Strategic Focus Areas

Regulatory

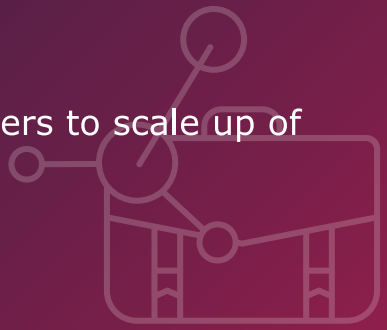
- Promote clear, predictable, and efficient regulatory framework.
- Assess all FDA, EMA, and related guidance relevant to cell and gene therapy, including guidance related to manufacturing, CMC, and related issues.
- Promote international convergence of key regulation and guidance to promote global product development by identifying specific areas of regulatory inconsistency among jurisdictions and developing proposals for adoption by regulatory agencies.

Reimbursement

- Develop principles of ARM-endorsed global value framework.
- Develop strategies to remove or mitigate barriers via regulatory changes or legislation for public and private payers both in the U.S. and in key EU countries.
- Secure favorable access and reimbursement for RM / AT products.

Industrialization and Manufacturing

- Reduce standards, technical, and regulatory barriers to scale up of RM / AT therapies.



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