Q3

ALLIANCE for Regenerative Medicine

2015

Quarterly Data Report

Regenerative Medicine & Advanced Therapies

ALLIANCE for
Regenerative Medicine

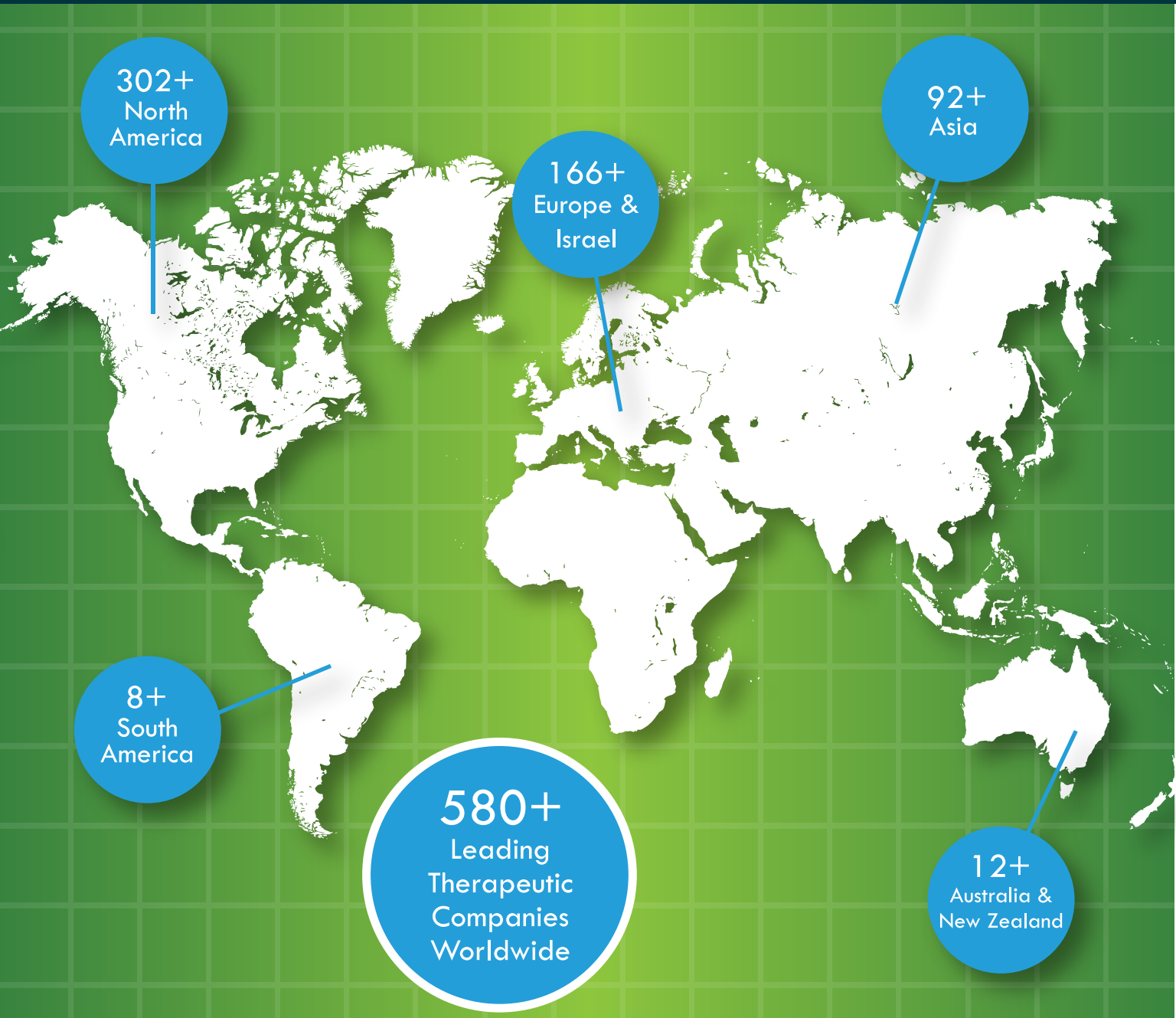
The Alliance for Regenerative Medicine (ARM) is the preeminent global advocate for regenerative and advanced therapies. ARM fosters research, development, investment and commercialization of transformational treatments and cures for patients worldwide.

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.

alliancerm.org

Table of Contents

Industry Overview



Industry Overview

Regenerative medicine companies held their ground throughout the third quarter in terms of new IPOs, M&As, financing rounds and partnerships, while bad news abounded in other areas of healthcare.

This recent quarter saw Immunocore Limited raising $320 million in a private financing round to move their bispecific biologic IMCgp100 program into the next phase, while REGENXBIO, NantKwest, Kiadis Pharma and Benitec BioPharma all closed successful IPOs. AVAX Technologies reported its plan to raise a $45 million Series A round to move its autologous cell vaccine immunotherapy (AC Vaccine) into the clinic, while Fibrocell Science and Intrexon completed secondary rounds ($17.2 million and $230 million, respectively) and Baxalta announced a secondary filing for up to $1.45 billion of common stock. Additionally, Juno received FDA clearance for their IND application, allowing the company to initiate a multi-center, pivotal Ph II trial evaluating their CAR-T therapy (JCAR015) in patients with relapsed or refractory acute lymphoblastic leukemia.

The third quarter also saw numerous partnerships and licensing agreements, including AGTC's game-changing collaboration with Biogen involving its AAV-based gene therapies for the treatment of rare eye diseases. This deal came with an upfront payment of $124 million and includes milestone payments that have the potential to exceed $1 billion. Sanofi struck a deal with Evotec to collaborate on the development of a beta cell replacement therapy, as well as developing human beta cells for high-throughput drug screening and AstraZeneca entered into a license agreement between MedImmune and Inovio Pharmaceuticals for INO-3112, targeting human papillomavirus types 16 and 18.

Several notable acquisitions took place in the third quarter, beginning with TiGenix's acquisition of Coretherapix in a deal valued at up to $318.5 million. Another significant deal this quarter was AMAG Pharmaceuticals' mid-August acquisition of Cord Blood Registry for $700 million.

Overall, there is increasing activity by regenerative medicine companies participating in the numerous partnering and investor conferences taking place this fall. Investors of all types, from institutional and pharma fund managers to venture capitalists and angels, are carefully monitoring new advances as the field gains ground and credibility. As the final quarter of 2015 begins, we look forward to reviewing innovative therapies throughout the regenerative medicine arena.

– Patricia Reilly
Executive Director – Medtrack

– Nancy Dvorin
Managing Editor – IN VIVO, Start-Up and Medtech Insight

Informa Business Intelligence,
Pharma and Healthcare

Financings

Total Financings: $2.8B Q3 2015
$9.3B YTD Q3 2015
Up 163% compared to YTD Q3 2014

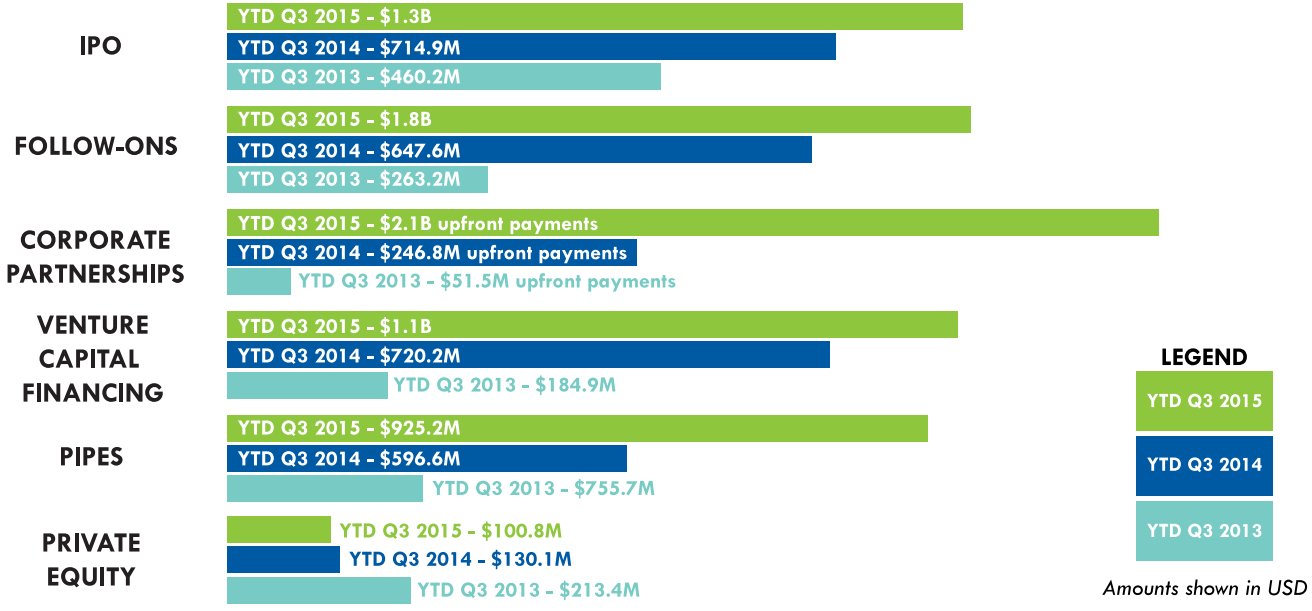
Gene & Gene-Modified Cell Therapy: $1.0B Q3 2015
$5.7B Raised YTD Q3 2015
Up 137% compared to YTD Q3 2014

Tissue Engineering: $340.5M Q3 2015
$631.3M Raised YTD Q3 2015
Up 258% compared to YTD Q3 2014

Cell Therapy: $1.9B Q3 2015
$6.3B Raised YTD Q3 2015
Up 198% compared to YTD Q3 2014

**Total amount raised represents sector-wide figures; please note that some companies are active in 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.*

Total financings by type: YTD Q3 2015



Amounts shown in USD

Total M&A: YTD Q3 2015

Examples of key financings: Q3 2015

IPOs:

- REGENXBIO closes $159.4M initial public offering – September 22, 2015
- NantKwest, Inc. closes $238.3M initial public offering – July 31, 2015
- Kiadis Pharma closes $36.5M initial public offering – July 2, 2015

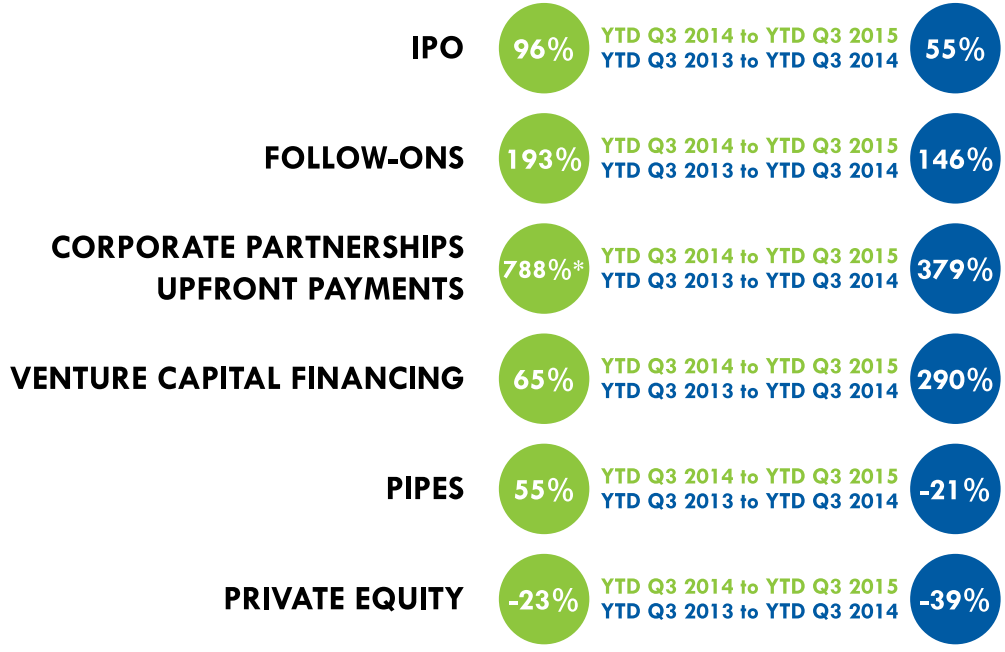
FOLLOW-ONS:

- Intrexon Corporation closes $230M underwritten public offering – August 26, 2015
- Fibrocell Science closes $17.2M public offering of common stock – July 27, 2015

VENTURE FINANCINGS:

- Intellia Therapeutics, Inc. raises $70M in Series B financing – September 1, 2015
- Immunocore Limited raises $320M in private financing round – July 16, 2015

Financing Comparisons: YTD Q3 2015



*Year-to-date, there have been six partnership deals in 2015 with $100M+ upfront payments.

Sector Commentary

Adam Bristol
Analyst & Director of Research
Aquilo Capital, L.P.

Fariba F. Ghodsian
Chief Investment Officer
DAFNA Capital Management, LLC

Daniel Krizek
Director
Brookside Capital

Given the volatility in the global markets, do you remain optimistic that the financing window will remain open for gene therapy?

The capital markets can be fickle, but I'm an optimist by nature. My general belief is that true innovation will always attract funding, whether it be from VCs, strategic pharma partners, the public markets or government grants. The first approval of a gene therapy in the U.S. will be an important milestone, and the field appears to be achingly close. That first approval could provide the regulatory and commercial precedent needed to support other programs in the space. – AB

Obviously, the broader financing climate for biotechnology companies impacts gene therapy companies. However, we remain encouraged by the continued progress in the sector for a variety of diseases and the potential approval of the first gene therapy product for inherited retinal dystrophies, events that should sustain investor interest in financing gene therapy companies. – FG

A company's ability to raise money is driven by both the market conditions and the company's specifics. Financial markets is a cyclical industry, and no subsector, including gene therapy, is immune to the fluctuations. There will be times when financing conditions are more favorable, and when they are less, and it's hard to predict. But the rest is company-specific. A company that just generated strong clinical data will be in a better position to finance itself than a company that did not. There are many gene therapy companies running trials – the financing window, at least partially, will depend on outcomes of those trials. – DK

What makes you optimistic that gene therapy companies can overcome the market access and commercialization hurdles ahead?

Numerous biotech and pharmaceutical companies are working hard to build the infrastructure needed to support the development and commercialization of several new therapeutic modalities, including gene therapy. Will there be challenges ahead? Certainly. But it seems to me that gene therapy is coming of age at a time when healthcare reform is in motion, and that confluence provides a tremendous opportunity. As with new products in any category, the value must be there to justify the price. Gene therapy offers the promise of durable treatments for many challenging diseases. If that promise is fulfilled, our society and our healthcare system will find a way to make those treatments available to the patients who need them. – AB

Several issues such as large-scale manufacturing, concerns of irreversibility in case of adverse events and complex reimbursement may hamper commercialization of gene therapies. However, we believe these concerns may be mitigated by the therapeutic benefit that these innovative treatments provide for patients and by addressing unmet medical needs where there is no alternative treatment. – FG

(continued from page 6)

People talk about commercialization hurdles ahead simply because of the novelty of gene therapy. There are no approved gene therapies in the U.S. yet. Manufacturing at scale is a question. Pricing is a question, especially if we're talking about one-time dose that leads to a cure. But in the end, these are mostly logistical issues. As long as the new gene therapy drugs work and are changing patients' lives, the logistics will get resolved. – DK

From your perspective, how important is large pharma participation in the gene therapy sector? Is their support/investment critical to long-term success?

Pharma participation is critical today, but it may not be in the future. As it stands, small, innovative biotech companies in a favorable funding environment can move a gene therapy program through development. Only pharma, however, has the resources to scale a gene therapy platform to many disease areas globally. We've seen several important biopharma alliances in the past few years, which I think is great. That said, a reliance on pharma could change very quickly. In the past decade, we've seen several biotech companies achieve success on a first marketed product, grow to have a global footprint and become acquirers of novel technologies, just like traditional pharmas. – AB

Pharma support is important both for validating gene therapy as a broader therapeutic modality and for providing manufacturing and financial support. One large pharma, Novartis, is at the forefront of CAR-T utilizing gene therapy to combat cancer. We have also been encouraged by collaborations with larger biotech companies to facilitate the development of gene therapies for orphan diseases. – FG

Pharma participation is generally important – they have larger R&D budgets, large domestic and international footprints and vast experience with regulatory issues. They can potentially create a lot of value for both early- and late-stage products, accelerate development, commercialize abroad, etc. Of course, there are plenty of small companies who decided to go alone and eventually succeeded. For many others, however, partnership with a large pharma company was critical. Time will tell which way gene therapy goes. – DK

Clinical Trials

571 Clinical trials underway

Ph. I: 183
Ph. II: 331
Ph. III: 57

74 Approved and/or marketed products

As of Q3 2015, there are 74 RM / AT products available on the market – many approved to be marketed only in specific regions and/or countries.

This list includes products reviewed and approved by internationally-recognized regulatory agencies, as well as products brought to market in the U.S. under The Food, Drug and Cosmetic Act and The Public Health Service Act. A list with examples of approved and/or marketed RM / AT products is available on ARM's website – www.alliancerm.org.

Current Clinical Trials by Therapeutic Category: Q3 2015

- More than 37% of current clinical trials are in oncology
- More than 13% are in cardiovascular

	Cardiovascular 76		Musculoskeletal 39		Dermatology 33		Immunology & Inflammation 24	
Oncology 214		Infectious Disease 42		Central Nervous System 38		Ophthalmology 33		Endocrine, Metabolic & Genetic Disorders 22
	Hematology 12		Respiratory 5		Ear Diseases 2		Radiation Injury 1	
Gastroenterology 15		Surgery 9		Genitourinary Disorders 4		Lymphatic Diseases 1		Dental 1

Corporate Partnerships, Acquisitions & Key Data Events

Examples of key corporate partnerships & acquisitions: Q3 2015

AMAG Pharmaceuticals acquires Cord Blood Registry for $700M	August 17, 2015
Inovio Pharmaceuticals enters into $727.5M strategic cancer vaccine collaboration and license agreement with MedImmune	August 10, 2015
TiGenix acquires Coretherapix in a deal valued at up to $318.5M	July 30, 2015
Integra LifeSciences acquires TEI Biosciences and TEI Medical for $312M	July 20, 2015
Biogen signs agreement with AGTC valued at up to $1.1B for ophthalmology gene therapies	July 2, 2015

Examples of major milestones and key data events: Q3 2015

- BioTime subsidiary Cell Cure Neurosciences Ltd. receives Fast Track designation from the FDA for OpRegen for the treatment of the dry form of age-related macular degeneration – September 28, 2015
- Mesoblast Limited licensee JCR Pharmaceuticals Co. Ltd. receives full product approval in Japan – September 18, 2015
- Dimension Therapeutics, Inc. announces FDA Fast Track designation for lead candidate DTX101 in patients with hemophilia B – September 17, 2015
- Amarantus BioScience Holdings, Inc. receives orphan drug designation from the FDA for MANF for treatment of retinal artery occlusion – September 14, 2015
- Audentes Therapeutics, Inc. receives orphan drug designation from the FDA and EMA for AT001 for the treatment of x-linked myotubular myopathy – August 26, 2015
- TiGenix announces Cx601 meets primary endpoint in pivotal phase III ADMIRE-CD trial in Crohn's patients with complex perianal fistulas – August 23, 2015
- TxCell receives Fast Track designation from FDA for lead product Ovasave for the treatment of moderate to severe Crohn's disease – July 27, 2015

Cell Therapy Clinical Outlook

Eduardo Bravo
CEO
TiGenix

Michael Hunt
Chief Financial Officer
ReNeuron

Karine Kleinhaus
Divisional Vice President,
North America
Pluristem Therapeutics

Chaim Lebovits
President & CEO
BrainStorm Cell Therapeutics

Please provide an overview of your current clinical programs, indications and stages of development.

Brainstorm Cell Therapeutics:

Our lead NurOwn® program is in ALS, which is now well into Ph II. We completed two single arm studies that enrolled a total of 26 ALS patients and demonstrated not only the safety and tolerability of a single dose of NurOwn, but showed encouraging signs of efficacy, substantially reducing the rate of disease progression. We recently completed treatment of all 48 patients in our first U.S. trial, a double-blind, placebo-controlled trial conducted at three prestigious academic medical centers – Massachusetts General Hospital, University of Massachusetts and the Mayo Clinic in Rochester.

Pluristem Therapeutics:

Our first product, PLX-PAD, has been accepted into the EU's Adaptive Pathways Project for use in critical limb ischemia. Selection into this pathway provides us with high-level guidance as we submit a protocol for a Ph II trial to be used as the basis to apply for conditional marketing authorization in the EU for this indication. We expect to begin this Ph II trial in early 2016.

We are also applying to a regulatory pathway in Japan that allows for regenerative medicines to be considered for conditional marketing after a successful Ph II trial, targeting PLX-PAD for critical limb ischemia. Having completed a successful Ph II trial in muscle injury, we are exploring potential partnerships to develop PLX-PAD in additional orthopedic indications.

Our second product, PLX-R18, is moving forward in two indications: incomplete hematopoietic recovery following hematopoietic cell transplantation and acute radiation syndrome. We completed a successful pre-IND meeting with the FDA, are in the final stages of submitting a Ph I protocol, and expect to begin the trial in early 2016. We have completed a separate positive pre-IND meeting with the FDA for PLX-R18 in acute radiation syndrome. By end of the year 2015, we expect to submit a protocol for large animal trials and expect that the NIH will support and initiate them in early 2016.

ReNeuron:

We have three clinical-stage programs in progress currently. Our therapeutic candidate for stroke disability is in Ph II development, our candidate for critical limb ischemia is in Ph I and we are about to commence a Ph I/II study with our candidate for the blindness causing disease retinitis pigmentosa.

TiGenix:

Our most advanced asset is Cx601, a local injection of allogeneic expanded adipose-derived stem cells for the treatment of complex perianal fistulas in Crohn's disease patients. This August, we announced positive results of the EU Ph III trial and we are planning on filing for marketing approval in Q1 2016. The product could be launched in Europe by the second half of 2017. Also in August, we received a positive SPA for our U.S. Ph III trial, which we plan to start in Q1 2017.

Our second product is Allo-CSC-01, an intracoronary injection of allogeneic cardiac stem cells, finalizing the recruitment of a Ph II trial in patients who have suffered a myocardial infarct. Interim six-month data will be available next summer and the full one-year data will be available in spring 2017.

We also have Cx611, an intravenous administration of eASCs. We are planning to start a Ph II trial in severe sepsis at the end of this year.

Please tell us about the year ahead for your company – plans, clinical milestones and other anticipated developments.

BrainStorm Cell Therapeutics:

We are preparing to launch our first multi-dose study of NurOwn to ALS patients, and we hope that multiple doses will extend the kinds of benefits we've seen thus far. We will also have data from the Ph II U.S. study in 2016. We are also working on moving additional indications into the clinic, including progressive MS and autism, and working to expand our preclinical pipeline with new indications. Additionally, we expect to implement some important initiatives to support an expanded manufacturing capacity.

Pluristem Therapeutics:

In early 2016, we expect to begin a Ph II trial that could lead to conditional marketing in the EU for PLX-PAD in critical limb ischemia.

(continued page 11)

Cell Therapy Clinical Outlook

(continued from page 10)

We also expect to begin a Ph II trial in Japan targeting conditional marketing for PLX-PAD in critical limb ischemia. In early 2016, we plan to begin a Ph I trial of PLX-R18 in incomplete hematopoietic recovery following hematopoietic cell transplantation. As well, we believe that in the first half of 2016, the NIH's NIAID will begin a large animal trial for PLX-R18 in acute radiation syndrome, under the FDA's Animal Rule regulatory pathway. In early 2016, we expect to complete recruitment for our ongoing Ph II study in intermittent claudication, and anticipate that United Therapeutics will announce data from their Ph I trial of PLX-PAD in pulmonary arterial hypertension in 2016.

ReNeuron:
We will shortly commence a Ph I/II clinical trial in the U.S. with our cell therapy candidate for retinitis pigmentosa. During 2016, we also expect to garner Ph II data from our ongoing UK clinical trial in disabled stroke patients and we are also due to commence a Ph II study with our critical limb ischemia candidate during 2016, once the current Ph I study has completed. In addition, very soon, we will relocate to a new state-of-the-art facility in South Wales. With our recently completed $105m equity financing, we are well-funded and well-placed to pursue these endeavors.

TiGenix:
For Cx601, we are planning to file for European marketing authorization in Q1 2016, with the expectation of receiving EU marketing approval in Q1 2017. In the U.S., we are planning on finalizing our tech transfer to Lonza to manufacture Cx601 for our U.S. Ph III clinical trial. We will then file the IND and start recruitment for the trial in Q1 2017.

For Allo-CSC-01, we will finalize recruitment of our ongoing Ph II trial before year's end. This will allow us to have interim six-month data in by the summer of 2016. In addition, for Cx611, we will be enrolling patients in our Ph II trial in severe sepsis.

What makes you optimistic about the outlook for cell therapy and its potential to bring transformative treatments/cures to patients?
BrainStorm Cell Therapeutics:
Cell therapies may have the potential to treat diseases that other kinds of therapeutics – small molecules or antibodies, for example – might not be able to treat. With neurodegenerative diseases in particular, we believe that cell therapies might be able to replace dead or dying cells, and, in the case of NurOwn, provide a comprehensive support environment by delivering a variety of neurotrophic factors, as well as immunolomodulatory effects, to stressed, diseased or damaged neurons.

Pluristem Therapeutics:
As populations age, there will be a growing demand for older generations to maintain functionality and the capacity to enjoy daily activities. Cell therapies target a range of severe unmet medical needs, many of which are more common in older populations. Innovative cell therapies could also help people of all ages suffering from a range of serious diseases with limited treatment options.

I believe that allogeneic cell therapies, as compared to autologous therapies, may enable care providers to deliver transformative treatments to a broader segment of the population, as off-the-shelf products are likely to be easier to administer than those that are patient-specific. However, I anticipate that both allogeneic and autologous cell therapies will come into their own and will transform the therapeutic landscape in the coming years.

ReNeuron:
ReNeuron was founded on our belief in the potential of cell therapy to address significant unmet medical needs with highly novel treatments. Despite the significant challenges this presents to those like us who look to realize the clinical and commercial potential of cell therapy, we are very positive on the outlook for the sector as it matures and exciting new cell therapy treatments emerge.

TiGenix:
It's been a long journey, but we're getting there! Data from several large trials will be available shortly and we are hopeful that, like for Cx601, some will be positive and will lead to approvals for cell therapy products across various regions. As more good news is shared, we're optimistic that this field will attract even more attention and resources.

Current Regulatory & Legislative Priorities

- **Advocating for reimbursement coverage and coding policies for regenerative medicine and advanced therapies products,** promoting a supportive and incentivizing payment structure. This includes developing several white papers on key reimbursement issues, identifying barriers to coverage and payment, recommending policy solutions.

- **Gene editing technologies and germline modification.** Given the significant safety and ethical implications of modifying the DNA of human reproductive (germline) cells, ARM has called for a voluntary worldwide moratorium on this kind of research to allow for rigorous and transparent legal and policy discussions and a multi-stakeholder debate regarding the science, safety and ethics of modifying germline cells.
  A meeting to discuss this issue has been organized by the U.S. National Academy of Science and the U.S. National Academy of Medicine, joined by the Chinese Academy of Sciences and the U.K. Royal Society, scheduled for December 1-3, 2015 in Washington, D.C.

- **21st Century Cures Act/Medical Innovation legislation.** Following the U.S. House of Representatives' passage of the 21st Century Cures Act earlier this year, the U.S. Senate is currently working on its companion bill. ARM is involved in extensive discussions to promote ARM's priorities and ensure their inclusion in the Senate's bill language, including:
  - *Standards Coordinating Body for regenerative medicine and advanced therapies.* This organization would work closely with global standards agencies, creating a central clearinghouse for the coordination, development, communication and implementation of technical and process standards and best practices.
  - *Gene therapy clinical trials.* ARM is advocating a modified role for the NIH Recombinant DNA Advisory Committee (RAC) to ensure the oversight of trials is streamlined.
  - *Expedited approval pathway.* In order to improve the efficiency of the approval pathway for regenerative medicine and advanced therapies products, ARM is advocating that the FDA designate certain RM / AT products as "Qualified Regenerative Medicine Products" (QRMP), intended for serious and life-threatening diseases with currently no available treatment options. The FDA would meet with the QRMP sponsors to discuss expedited review options.
  - *Combination products.* ARM advocates for reforms to streamline the review process for combination products or other situations when more than one review center at FDA is involved in product evaluation and review.

- **PDUFA reauthorization.** The current Prescription Drug User Fee Act (PDUFA) version V is set to expire in 2017. ARM has submitted comments advocating for a Standards Coordinating Body, QRMP designation and improved coordination and communication among FDA review centers. ARM is forming a PDUFA working group to identify other issues.

- **European Commission's GMP requirements for ATMP.** ARM is reviewing and preparing comments in response to the European Commission's stakeholder consultation on guidelines of good manufacturing practice (GMP) requirements for Advanced Therapies Medicine Products (ATMP). ARM comments will focus on the way this guide will integrate the rules governing medicinal products in the European Union, on the application of a risk-based approach for defining requirements for commercial and investigational ATMP, as well as ensuring international harmonization of requirements between the U.S. and the EU, in addition to other regions.

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ALLIANCE for Regenerative Medicine

Alliance for Regenerative Medicine
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