Evolving Landscape of Cell & Gene Therapies

Cell & Gene Connect

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ARM's Role in the Sector

- Advocating for clear, predictable, and harmonized regulatory and review 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 and identifying sources of potential public funding

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Sector Overview

- **Policy Environment:** 2018
- **Sector Technology Overview:** 2018
- **Clinical Progress:** 1H 2018
- **Anticipated Clinical Data Events:** 2018-2019
- **Looking ahead:** 2019 and beyond

A Quick Note -

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This presentation will be available via:

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

Supportive Policy Environment – United States

- FDA:
  - RMAT designation
  - FDA's 6 new draft guidances for gene therapy
  - 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

- NIH:
  - Recent proposal to limit the NIH and its Recombinant DNA Advisory Committee (RAC) in the review of human gene therapies to reduce overlap between FDA and NIH oversight

- CMS:
  - Actively participate in conversations with therapeutic developers about alternate payment models

- Congress:
  - The House of Representatives' Health Care Innovation Caucus has requested stakeholder input on experiences and recommendations regarding value-based reimbursement models

Supportive Policy Environment – EMA and EC

- European Commission and EMA developed a joint ATMP plan of actions, with ARM providing input on proposals. The actions include:
  - Reduce discrepancies across the EU regarding the application of GMO rules to ATMPs containing or consisting of GMOs (gene therapies).
  - Revision of EMA procedures regarding the assessment of ATMPs to reduce administrative burden and address specific needs of ATMP developers
  - Provide enhanced scientific support for the development of ATMPs (ongoing as part of PRIME)
  - Address hospital exemption different interpretations in different MS and discuss different options
  - Revision of the EMA Guideline on Safety and Efficacy and Risk Management Plans for ATMPs to reduce administrative burden in the post- marketing phase

- The European Commission has proposed new European legislation aimed at coordinating some health technology assessment activities - namely clinical assessments - at the European level, with the potential to create increased international harmonization and reduced duplication of efforts when companies apply for HTA of their products.

Policy Makers Actively Seeking Guidance in Regenerative Medicine

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ARM's Recent Comments, Letters, & Testimony	Purpose	Recipient	Date
Comments on EMA 'Draft qualification opinion on Cellular therapy module of the EBMT Registry'	Provide recommendations to improve the use of the EBMT registry as a source of long-term follow-up data for the use of CAR-T products	EMA	Aug. 2018
Letter to CBER recommending future disease specific guidances that should be issued	Ask the FDA to consider a number of factors when prioritizing future disease-specific guidances for cell and gene therapies & disease areas that could benefit from further guidance from the FDA	FDA/CBER	Aug. 2018
Response to the House of Representatives' Health Care Innovation Caucus	Provide information regarding value-based payment reform and value-based arrangements	Congress	Aug. 2018
Position statement on the proposed Regulation amending Directive 2011/24/EU (COM(2018) 51 final)	Provide key recommendations intended to ensure the success of the proposed joint HTA in order to facilitate market access and promote convergence of requirements	EC, EP, NCAs	July 2018
Comment on Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs	Encourage HHS to consider the potential value of cell and gene therapies to patients and society, and the need to enable new pricing and reimbursement approaches that can help make them available to patients	HHS	July 2018
Comment on Medicare Hospital Inpatient Prospective Payment Systems	Encourage appropriate payment for innovative therapies, identify concerns with CMS criteria for NTAP eligibility, and urge CMS to implement a more frequent NTAP approval process	CMS	June 2018
Comment on National Coverage Analysis Tracking Sheet for CAR-Ts	Request that CMS rescind the planned NCA; also identified several issues that CMS is encouraged to address if NCA were to continue forward	CMS/CAG	June 2018
Submission of comments on EMA 'Guideline on safety and efficacy follow-up and risk management of ATMPs'	Request clarification throughout the guidance document & suggests the creation of a separate document for pre-authorization safety expectations	EMA	April 2018

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Letter to CBER regarding gene therapy (GT) guidance announcement	Request clarification on disease selection, expert input, end point selection, patient reported outcomes and clinical trials in forthcoming gene therapy guidance.	FDA/CBER	March 2018
Position on possible solutions to foster development and expand patient access for ATMPs in Europe	Provide additional recommendations to support and complement EMA/EC Action Plan on ATMPs	EMA, EC	March 2018
Comment on FDA Draft Guidance for Industry: "Expedited Programs for Regenerative Medicine Therapies for Serious Conditions"	Request clarification regarding terminology and definitions used in RMAT designation, as well as advantages of RMAT vs. Breakthrough Therapy designations	FDA	March 2018
Comment on FDA Draft Guidance "Chemistry, Manufacturing, & Controls Changes to an Approved Application: Certain Biological Products"	Encourage FDA to recommend a risk-based approach for CMC changes that takes the level of evidence and internal quality systems into account in determining when the appropriate reporting category for all post approval alterations; request additional feedback from FDA to specify C&GT products not covered by this guidance	FDA	March 2018
Comment on FDA Draft Guidance: "Evaluation of Devices Used with Regenerative Medicine Advanced Therapies"	Support streamlined FDA application of the regulatory requirements for devices intended for use with RM / AT therapies	FDA/CBER	Feb. 2018
Public Testimony regarding NTAP program	Suggest improvements to CMS's NTAP program, including the payment rate & the criteria used to award additional payments	CMS	Feb. 2018
Response to OIG Solicitation of New Safe Harbors and Special Fraud Alerts	Express the need for an anti-kickback safe harbor to facilitate value-based purchasing agreements	OIG/HHS	Feb. 2018

FDA's RMAT Designation

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:

- In early 2017, FDA published application instructions.
- ARM's February RMAT webinar for members included FDA officials.
- ARM advocated that gene therapies qualify; FDA confirmed late 2017.
- 21 products have publicly announced they have received the designation (as of mid-August 2018).

FDA's RMAT Designation

1. Abeona EB-101 (recessive dystrophic EB)
2. Abeona ABO-102 AAV gene therapy (MPS IIIA)
3. Asterias's AST-OPC1 (spinal cord injury)
4. Athersys's MultiStem (ischemic stroke)
5. Audentes Tx's AT132 (X-Linked Myotubular Myopathy)
6. bluebird bio's LentiGlobin (severe sickle cell disease)
7. Caladrius's CD34+ cell therapy (refractory angina)
8. Capricor CAP-1002 (Duchenne muscular dystrophy)
9. Cellerant's Romyelocel-L cell therapy (treatment of infection)
10. Cellvation's CEVA101 (traumatic brain injury)
11. Enzyvant's RVT-802 (DiGeorge syndrome)
12. Humacyte's Humacyl (vascular access for hemodialysis)
13. jCyte's jCell (retinitis pigmentosa)
14. Juno's JCAR017 (r/r aggressive large B cell NHL)
15. Kiadis's ATIR101 (leukemia)
16. Mallinckrodt's Stratagraft (deep partial-thickness burns)
17. Mesoblast's MPC-150-IM (heart failure)
18. MiMedx's AmnioFix (osteoarthritis of the knee)
19. Nightstar Tx's NSR-REP1 (choroideremia)
20. Vericel's ixmyelocel (dilated cardiomyopathy)
21. Voyager Tx's VY-AADC (Parkinson's Disease)

ARM's Current Legislative & Regulatory Priorities

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CMC Goals

- Assess all FDA and EMA CMC guidance relevant to cell and gene therapy, working to modify, revise or propose guidance provisions as appropriate
- Lead a consortium to produce a case study based white papers advising on CMC challenges for both cell therapy and gene therapy product development

Regulatory Goals

- 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.
- Drive international convergence of key regulation and guidance to promote global product development by identifying specific areas of regulatory inconsistency.

Reimbursement Goals

- Develop principles of ARM-endorsed global value framework.
- Enact 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.

Clinical Progress 2018 & Beyond

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.

Total Clinical Trials by Phase as of Mid-Year 2018

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Phase I

324

Phase II

560

Phase III

93

Source data provided by: informa

Total Clinical Trials by Technology Type Phase as of Mid-Year 2018

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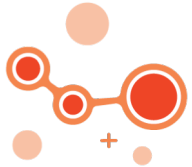
Gene Therapy

Total: 317

Phase I: 109

Phase II: 174

Phase III: 34



Gene-Modified Cell Therapy

Total: 314

Phase I: 134

Phase II: 166

Phase III: 14

Cell Therapy

Total: 322

Phase I: 76

Phase II: 208

Phase III: 38

Tissue Engineering

Total: 24

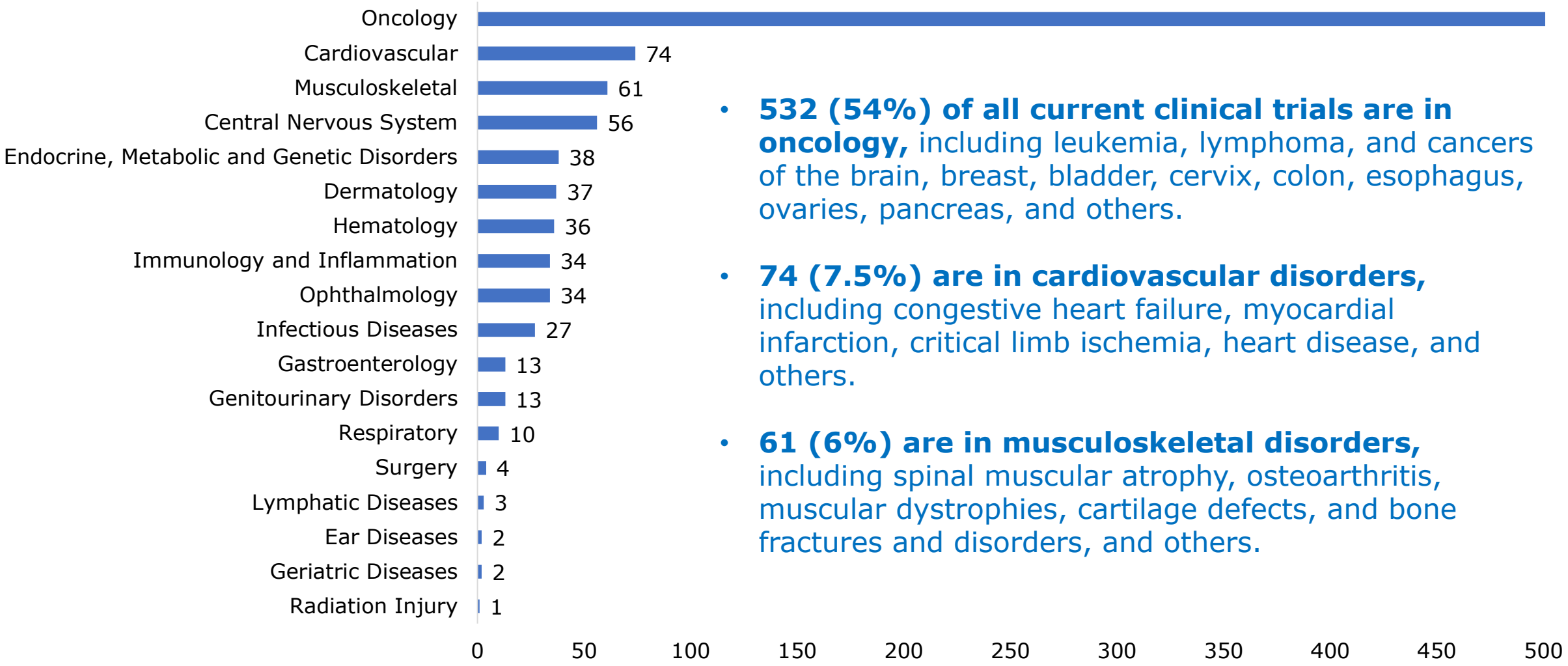
Phase I: 5

Phase II: 12

Phase III: 7

Source data provided by: informa

Clinical Trials by Therapeutic Category



- **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, and others.

Source data provided by: informa

Recent Product Approvals

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Approvals YTD 2018:

- 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

Approvals in 2017:

- Spark Therapeutics' **LUXTURNA** gene therapy for biallelic RPE65-mediated inherited retinal disease – Dec 19; MAA submitted to EMA – July 31
- Gilead / Kite Pharma's **Yescarta** CAR T-cell therapy for the treatment of adult patients with relapsed/refractory large B-cell lymphoma after two or more lines of systemic therapy – Oct 18;
- Novartis's **Kymriah** CAR T-cell therapy for the treatment of children and young adults with relapsed or refractory B-cell acute lymphoblastic leukemia and for adults with r/r diffuse large B-cell – August 30; MAA submitted to EMA – Nov 6
- TissueGene's (now Kolon TissueGene) exclusive Asia licensee Kolon Life Science's **Invossa-K Inj** – July 12

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	2H 2018; launch 2019
bluebird bio	Lentiglobin	Gene therapy	Transfusion dependent beta-thalassemia	MAA filing	New data was presented in June 2018; on track to submit MAA in 2H 2018
Enzyvant Tx	RVT-802	Tissue-based therapy	Complete DiGeorge Syndrome	BLA submission	Enzyvant announced 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
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
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
Bone Therapeutics	PREOB	Cell therapy (autologous)	Osteonecrosis of the hip	Ph III	Interim results expected 2H 2018

Source: Company-provided or publicly-available information

Select Anticipated Late-Stage Data Events: 2018+

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bluebird bio	Lenti-D	Gene therapy	Cerebral Adrenoleukodystrophy	Ph III – Starbeam 102	End-year 2018
Bone Therapeutics	PREOB	Cell therapy (autologous)	Osteonecrosis of the hip	Ph III	Interim results expected 2H 2018
Brainstorm	NurOwn	Mesenchymal Stem Cell Therapy	ALS	Ph III	Topline results expected late 2019
Cytori	ECCI-50	Cell therapy	Male stress urinary incontinence	Ph III	Data anticipated in 1H 2019
Cytori	Habeo	Cell therapy	Hand scleroderma	Ph III	Planned data readout 2H 2018
Mesoblast	MPC-150-IM	Mesenchymal Precursor Cell Therapy	Mod to Severe Chronic Heart Failure	Ph III	Complete enrollment 2H CY 2018
Mesoblast	MSC-100-IV	Mesenchymal Stem Cell Therapy	Acute Graft Versus Host Disease	Ph III	Day 180 safety data Q3 CY18
Mesoblast	MPC-06-ID	Mesenchymal Precursor Cell Therapy	Chronic Low Back Pain Due to Disc Degeneration	Ph III	Enrollment in the trial completed in Q1 2018
Nightstar Therapeutics	NSR-REP1	Gene therapy	Choroideremia	Ph III	Complete enrollment 1H 2019
Pfizer	Fidanacogene elaparvovec	Gene therapy	Hemophilia B	Ph III	Initiated trial July 2018

Source: Company-provided or publicly-available information

Key Takeaways

Supportive policy environment:

- U.S. and globally

Strong scientific data:

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

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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Pharma Intelligence | Informa

- Global landscape
- M&A Transactions
- Key partnerships
- Global financings
- Commercialization challenges overview
- Key initiatives to address