Gene, Cell, & RNA Therapy Landscape

Q1 2022 Quarterly Data Report
About the authors

The American Society of Gene & Cell Therapy (ASGCT) is the primary professional membership organization for scientists, physicians, patient advocates, and other professionals with interest in gene and cell therapy.

Our members work in a wide range of settings including universities, hospitals, government agencies, foundations, biotechnology and pharmaceutical companies. ASGCT advances knowledge, awareness, and education leading to the discovery and clinical application of gene and cell therapies to alleviate human disease to benefit patients and society.

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With more than 400 analysts, journalists, and consultants keeping their fingers on the pulse of the industry, no key disease, clinical trial, drug approval or R&D project isn’t covered through the breadth and depth of data available to customers. For more information visit pharmaintelligence.informa.com.
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Introduction

Welcome to the first quarterly report of the year from ASGCT and Informa Pharma Intelligence. We’re excited to share the highlights of Q1 2022, including approval of a new CAR T-cell therapy to treat multiple myeloma in the U.S. and filing for approval of an AAV5 gene therapy to treat hemophilia B in the EU and the UK. Additionally, an RNA therapy was approved to treat coronavirus in Australia and South Korea.

This quarter, 25% of newly initiated gene therapy clinical trials were for non-oncology diseases, falling from 35% in Q4 2021. In non-genetically modified cell therapy development, oncology and rare diseases continue to be the top targeted areas. CAR-T cell therapies continue to dominate the pipeline of genetically modified cell therapies, representing 49% of technology. Similar to Q4 2021, 98% of CAR T-cell therapies are in development for cancer indications.

Q1 2022 saw the lowest quarter total of deals signed within the last year, representing a 26% decrease from Q1 2021. Alliance volume remained flat and financings trended down. Start-up financing dropped to $507.8 million, while the number of companies raising seed or Series A financing stayed at 15. Overall, however, the gene, cell, and RNA therapy landscape continues to expand. The gene therapy pipeline has increased 16% since Q1 2021. In the pipeline, there are 3,579 gene, cell, and RNA therapies in development from preclinical through pre-registration stages.
Key takeaways from Q1 2022

One new genetically modified cell therapy has been approved since Q4 2021, and one new gene therapy has filed for approval

- Carvykti, a CAR-T cell therapy developed by Legend Biotech and Johnson & Johnson, was approved for multiple myeloma in the U.S.
- EtranaDez (etranacogene dezaparvovec), an AAV5 gene therapy developed by uniQure, filed for approval in the EU and UK for hemophilia B

The gene, cell and RNA therapy landscape has continued to expand into 2022

- In the past year since Q1 2021, the gene therapy pipeline (preclinical to pre-registration) has increased by 16%

Oncology and rare diseases are the most targeted therapy areas for RNA, gene, and non-genetically modified cell therapy pipeline development

- For RNA therapy and non-genetically modified cell therapies the majority of the rare diseases targeted are in the non-oncology space, while for gene therapies the majority are oncological

Start-up financing remained steady in Q1 2022

- Volume and value of the 16 Series A and seed financings done by gene, cell, and RNA therapeutic companies, worth an aggregate $507.8M, was virtually flat from the previous quarter
- Overall dealmaking total across alliance, acquisitions, and financings saw a 15% decline
- In the largest start-up financing, Cellino Biotech, a Harvard University spin-out, raised $80M to support its large-scale production of autologous and allogeneic cell therapies
Key highlights in Q1 2022
Approved gene, cell, and RNA therapies

Globally, for clinical use, there are:

• 19 gene therapies approved (including genetically modified cell therapies)
  • Since Q4 2021 there has been one new genetically modified cell therapy approval: Carvykti (Legend Biotech and Johnson & Johnson) in the U.S.
  • Due to the marketing authorization for elivaldogene autotemcel (Skysona) in the EU being officially withdrawn by the EMA, the status of this therapy has reverted from approved to pre-registration, as per the filing in the U.S. in 2021
• 17 RNA therapies approved
• 56 non-genetically modified cell therapies approved

Source: Pharmaprojects | Informa, April 2022
# Approved gene therapies as of Q1 2022 (1/2)

<table>
<thead>
<tr>
<th>Product name</th>
<th>Generic name</th>
<th>Year first approved</th>
<th>Disease(s)</th>
<th>Locations approved</th>
<th>Originator company</th>
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<tr>
<td>Gendicine</td>
<td>recombinant p53 gene</td>
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<td>Head and neck cancer</td>
<td>China</td>
<td>Shenzhen SiBiono GeneTech</td>
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<tr>
<td>Oncorine</td>
<td>E1B/E3 deficient adenovirus</td>
<td>2005</td>
<td>Head and neck cancer; nasopharyngeal cancer</td>
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<td>Shanghai Sunway Biotech</td>
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<td>Rexin-G</td>
<td>mutant cyclin-G1 gene</td>
<td>2006</td>
<td>Solid tumors</td>
<td>Philippines</td>
<td>Epeius Biotechnologies</td>
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<td>Neovascularen</td>
<td>vascular endothelial growth factor gene</td>
<td>2011</td>
<td>Peripheral vascular disease; limb ischemia</td>
<td>Russian Federation, Ukraine</td>
<td>Human Stem Cells Institute</td>
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<tr>
<td>Imlygic</td>
<td>talimogene laherparepvec</td>
<td>2015</td>
<td>Melanoma</td>
<td>US, EU, Australia</td>
<td>Amgen</td>
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<tr>
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<td>autologous CD34+ enriched cells</td>
<td>2016</td>
<td>Adenosine deaminase deficiency</td>
<td>EU, UK</td>
<td>Orchard Therapeutics</td>
</tr>
<tr>
<td>Kymriah</td>
<td>tisagenlecleucel-t</td>
<td>2017</td>
<td>Acute lymphocytic leukemia; diffuse large B-cell lymphoma</td>
<td>US, EU, UK Japan, Australia, Canada, South Korea</td>
<td>Novartis</td>
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<tr>
<td>Luxturna</td>
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<td>2017</td>
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<td>Yescarta</td>
<td>axicabtagene ciloleucel</td>
<td>2017</td>
<td>Diffuse large B-cell lymphoma; non-Hodgkin’s lymphoma; follicular lymphoma</td>
<td>US, EU, UK, Japan, Canada, China</td>
<td>Kite Pharma (Gilead)</td>
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<tr>
<td>Collategene</td>
<td>beperminogene perplasmid</td>
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<td>Critical limb ischemia</td>
<td>Japan</td>
<td>AnGes</td>
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<tr>
<td>Zolgensma</td>
<td>onasemnogene abeparvovec</td>
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<td>Novartis</td>
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<tr>
<td>Zynteglo</td>
<td>betibeglogene autotemcel</td>
<td>2019</td>
<td>Transfusion-dependent beta thalassemia</td>
<td>EU, UK</td>
<td>Bluebird Bio</td>
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<tr>
<td>Tecartus</td>
<td>brexucabtagene autoleucel</td>
<td>2020</td>
<td>Mantel cell lymphoma; acute lymphocytic leukemia</td>
<td>US, EU, UK</td>
<td>Kite Pharma (Gilead)</td>
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<td>Libmeldy</td>
<td>atidarsagene autotemcel</td>
<td>2020</td>
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<td>Orchard Therapeutics</td>
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<td>Breyanzi</td>
<td>lisocabtagene maraleucel</td>
<td>2021</td>
<td>Diffuse large B-cell lymphoma; follicular lymphoma</td>
<td>US, Japan</td>
<td>Celgene (Bristol Myers Squibb)</td>
</tr>
</tbody>
</table>

Source: Pharmaprojects | Informa, April 2022

Text highlighted in yellow represent new approvals during Q1 2022
## Approved gene therapies as of Q1 2022 (2/2)

<table>
<thead>
<tr>
<th>Product name</th>
<th>Generic name</th>
<th>Year first approved</th>
<th>Disease(s)</th>
<th>Locations approved</th>
<th>Originator company</th>
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<tbody>
<tr>
<td>Abecma</td>
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<td>2021</td>
<td>Multiple myeloma</td>
<td>US, Canada, EU, UK, <strong>Japan</strong></td>
<td>bluebird bio</td>
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<tr>
<td>Delytact</td>
<td>teserpaturev</td>
<td>2021</td>
<td>Malignant Glioma</td>
<td>Japan</td>
<td>Daiichi Sankyo</td>
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<tr>
<td>Relma-cel</td>
<td>relmacabtagene autoleucel</td>
<td>2021</td>
<td>Diffuse large B-cell lymphoma</td>
<td>China</td>
<td>JW Therapeutics</td>
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<td><strong>Carvykti</strong></td>
<td>ciltacabtagene autoleucel</td>
<td><strong>2022</strong></td>
<td>Multiple myeloma</td>
<td><strong>US</strong></td>
<td><strong>Legend Biotech</strong></td>
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Text highlighted in yellow represent new approvals during Q1 2022
## Approved RNA therapies as of Q1 2022 (1/2)

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<th>Product name</th>
<th>Generic name</th>
<th>Year first approved</th>
<th>Disease(s)</th>
<th>Locations approved*</th>
<th>Originator company</th>
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<tr>
<td>Exondys 51</td>
<td>eteplirsen</td>
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<td>Dystrophy, Duchenne muscular</td>
<td>US</td>
<td>Sarepta Therapeutics</td>
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<tr>
<td>Spinraza</td>
<td>nusinersen</td>
<td>2016</td>
<td>Muscular atrophy, spinal</td>
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<td>Ampligen</td>
<td>rintatolimod</td>
<td>2016</td>
<td>Chronic fatigue syndrome</td>
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<td>Tegsedi</td>
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<td>Amyloidosis, transthyretin-related hereditary</td>
<td>EU, UK, Canada, US, Brazil</td>
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<tr>
<td>Onpattro</td>
<td>patisiran</td>
<td>2018</td>
<td>Amyloidosis, transthyretin-related hereditary</td>
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<td>Vyondys 53</td>
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<td>Dystrophy, Duchenne muscular</td>
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<td>Waylivra</td>
<td>volanesorsen</td>
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<td>Ionis Pharmaceuticals</td>
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<tr>
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<td>BioNTech</td>
</tr>
</tbody>
</table>

*For COVID-19 vaccines, this includes emergency use authorization and full approvals

Source: Pharmaprojects | Informa, April 2022

Text highlighted in yellow represent new approvals during Q1 2022
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<th>Generic name</th>
<th>Year first approved</th>
<th>Disease(s)</th>
<th>Locations approved*</th>
<th>Originator company</th>
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<tbody>
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<td>Hyperoxaluria</td>
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<tr>
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<td>viltolarsen</td>
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<td>NS Pharma</td>
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<td>Leqvio</td>
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<td>Amondys 45</td>
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<td>Dystrophy, Duchenne muscular</td>
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<td>Nulibry</td>
<td>fosdenopterin</td>
<td>2021</td>
<td>Molybdenum cofactor deficiency</td>
<td>US</td>
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<td>Lagevrio</td>
<td>molnupiravir</td>
<td>2021</td>
<td>Infection, coronavirus, novel coronavirus</td>
<td>US, UK, Denmark, Ireland, India, Japan, Mexico, Morocco, Indonesia, Australia, South Korea</td>
<td>Ridgeback Biotherapeutics</td>
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*For COVID-19 vaccines, this includes emergency use authorization and full approvals

Source: Pharmaprojects | Informa, April 2022

Text highlighted in yellow represent new approvals during Q1 2022
<table>
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<th>Drug</th>
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<th>Indication</th>
<th>Molecule</th>
<th>Event Date</th>
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<td>Antiviral - Other Treatments</td>
<td>Cellular</td>
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<td>Orphan Drug Designation (U.S.)</td>
<td>Hereditary Transthyretin (hATTR) Amyloidosis With Polyneuropathy (Familial Amyloid Polyneuropathy)</td>
<td>Antisense</td>
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<td>4D-125</td>
<td>Fast Track Status</td>
<td>Retinitis Pigmentosa (RP) (Ophthalmology)</td>
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<td>C-CAR039</td>
<td>Regenerative Medicine Advanced Therapy (RMAT) Designation; Fast Track Status</td>
<td>Non-Hodgkin's Lymphoma (NHL)</td>
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<td>CT-103A</td>
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<td>Rolling NDA/BLA Initiated</td>
<td>Bone Marrow Transplant and Stem Cell Transplant</td>
<td>Cellular</td>
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<td>Gastric Cancer</td>
<td>Cellular</td>
<td>02/14/2022</td>
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<td>Viral Gene Therapy</td>
<td>02/16/2022</td>
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<td>Orphan Drug Designation (Europe)</td>
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<td>Viral Gene Therapy</td>
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<td>Approval (U.S.)</td>
<td>Multiple Myeloma (MM)</td>
<td>Cellular</td>
<td>02/28/2022</td>
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<td>Cellular</td>
<td>03/01/2022</td>
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<td>Acute Myelogenous Leukemia (AML)</td>
<td>Cellular</td>
<td>03/09/2022</td>
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<td>Cellular</td>
<td>03/10/2022</td>
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<td>Orphan Drug Designation (U.S.)</td>
<td>Adrenoleukodystrophy</td>
<td>Viral Gene Therapy</td>
<td>03/14/2022</td>
</tr>
<tr>
<td>CAR-T Therapy Program (WUGEN)</td>
<td>Orphan Drug Designation (U.S.)</td>
<td>Hematologic Cancer</td>
<td>Cellular</td>
<td>03/15/2022</td>
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<td>Orphan Drug Designation (U.S.)</td>
<td>Acute Myelogenous Leukemia (AML)</td>
<td>Cellular</td>
<td>03/17/2022</td>
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<td>EtranaDez</td>
<td>MAA Submission (Europe)</td>
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<td>Hemophilia A</td>
<td>Viral Gene Therapy</td>
<td>03/29/2022</td>
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</tbody>
</table>
Pipeline overview
Pipeline of gene, cell, and RNA therapies

3,579 therapies are in development, ranging from preclinical through pre-registration

- 1,986 gene therapies (including genetically-modified cell therapies such as CAR T-cell therapies) are in development, accounting for 55% of gene, cell, and RNA therapies
- 816 non-genetically modified cell therapies are in development, accounting for 22% of gene, cell, and RNA therapies

Source: Pharmaprojects | Informa, April 2022
Gene therapy pipeline

Gene therapy and genetically modified cell therapies
Gene therapy pipeline: Quarterly comparison

- The increase in preclinical development since Q4 2021 is the smallest quarterly increase since Q1 to Q2 2021, at 3%
- In Q1 2022 Amicus and Taysha saw reductions in their gene therapy R&D pipelines to focus on specific programs
- One new gene therapy has filed for approval in Q1 2022.

Therapies currently in pre-registration:
- valoctocogene roxaparvovec (BioMarin)
  - In the EU and UK
- lenadogene nolparvovec (Genethon, GenSight Biologics)
  - In the EU and UK
- nadofaragene firadenovec (Ferring, FKD Therapeutics, Trizell)
  - In the US
- eladocagene exuparvovec (PTC Therapeutics)
  - In the EU and UK
- elivaldogene autotemcel (bluebird bio)
  - In the US (due to the marketing authorization in the EU being officially withdrawn by the EMA, the status of this therapy has reverted to pre-registration, as per the US filing in 2021)
- etranacogene dezaparvovec (uniQure)
  - In the EU and UK

<table>
<thead>
<tr>
<th></th>
<th>Q1 2021</th>
<th>Q2 2021</th>
<th>Q3 2021</th>
<th>Q4 2022</th>
<th>Q1 2022</th>
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<tbody>
<tr>
<td>Preclinical</td>
<td>1,190</td>
<td>1,296</td>
<td>1,353</td>
<td>1,412</td>
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<tr>
<td>Phase I</td>
<td>225</td>
<td>269</td>
<td>264</td>
<td>248</td>
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<tr>
<td>Phase II</td>
<td>231</td>
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<tr>
<td>Phase III</td>
<td>27</td>
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<tr>
<td>Pre-reg</td>
<td>8</td>
<td>7</td>
<td>5</td>
<td>5</td>
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<tr>
<td>Total</td>
<td>1,711</td>
<td>1,835</td>
<td>1,890</td>
<td>1,941</td>
<td>1,986</td>
</tr>
</tbody>
</table>

Source: Pharmaprojects| Informa, April 2022

16 / Q1 2022
Source: Amicus April 2022 Corporate Presentation; Taysha Fourth Quarter and Full Year 2021 Financial Results and Corporate Update; Pharmaprojects| Informa, April 2022
Genetic modification: *In vivo* vs. *Ex vivo*

- As found in 2021, *ex vivo* genetic modification is most commonly used for gene therapies in pipeline development.
- In Q1 2022 *in vivo* delivery techniques were used in 27% of gene therapies, the same proportion as in Q4 2021.

Source: Cell and Gene Therapy dashboard | Informa, April 2022
Gene therapy breakdown: CAR-Ts continue to dominate pipeline in 2022

- CAR T-cell therapies remain the most common technology used in the pipeline of genetically modified cell therapies (preclinical through to pre-registration), representing 49%, followed by the “other” category, which includes a list of less commonly used technologies such as TAC-T, CAR-M, and TCR-NK.

- As found in Q4 2021, 98% of CAR-T cell therapies are in development for cancer indications. The remaining non-oncology indications include scleroderma, HIV/AIDS and autoimmune disease (unspecified).
Gene therapy pipeline: Most commonly targeted therapeutic areas

- Oncology and rare diseases continue to be the top areas of gene therapy development in both the overall pipeline (preclinical to pre-registration) and in the clinic (phase I to pre-registration).

- Development for rare diseases most commonly occurs in the oncology space, representing a majority of 52% compared to non-oncology rare disease gene therapy pipeline development.

Source: Pharmaprojects | Informa, April 2022

*figures based on indications in pipeline development only for each therapy
Gene therapy pipeline: Most common rare diseases targeted

- For the 1006 pipeline (preclinical to pre-registration) gene therapies which are being developed for rare diseases, eight out of the top 10 rare diseases are oncological.

- In the same order as in Q4 2021, the top five rare diseases for which gene therapies are being developed are:
  1. Myeloma
  2. Non-Hodgkin’s lymphoma
  3. Acute myelogenous leukemia
  4. B-cell lymphoma
  5. Ovarian cancer

Source: Pharmaprojects | Informa, April 2022

*figures based on indications in pipeline development only for each therapy*
Gene therapy pipeline: Most common targets

Of the gene therapies in preclinical trials through pre-registration in which targets are disclosed:

- CD19, B-cell maturation antigen (BCMA), also known as TNF receptor superfamily member 17, and CD22 molecule all remain the top 3 most common targets for oncology indications since Q4 2021
- Coagulation factor VIII remains the most common target for non-oncology indications and coagulation factor IX has risen to second most common since Q4 2021

<table>
<thead>
<tr>
<th>Oncology targets</th>
<th>Number of therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD19 molecule</td>
<td>141</td>
</tr>
<tr>
<td>TNF receptor superfamily member 17</td>
<td>62</td>
</tr>
<tr>
<td>CD22 molecule</td>
<td>36</td>
</tr>
<tr>
<td>membrane spanning 4-domains A1</td>
<td>24</td>
</tr>
<tr>
<td>mesothelin</td>
<td>24</td>
</tr>
<tr>
<td>glypican 3</td>
<td>19</td>
</tr>
<tr>
<td>erb-b2 receptor tyrosine kinase 2</td>
<td>18</td>
</tr>
<tr>
<td>cancer/testis antigen 1B</td>
<td>17</td>
</tr>
<tr>
<td>claudin 18</td>
<td>14</td>
</tr>
<tr>
<td>CD33 molecule</td>
<td>13</td>
</tr>
<tr>
<td>CD7 molecule</td>
<td>13</td>
</tr>
<tr>
<td>programmed cell death 1</td>
<td>11</td>
</tr>
<tr>
<td>Not available on LocusLink/Entrez Gene</td>
<td>10</td>
</tr>
<tr>
<td>C-type lectin domain family 12 member A</td>
<td>9</td>
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<tr>
<td>mucin 1, cell surface associated</td>
<td>9</td>
</tr>
<tr>
<td>CD276 molecule</td>
<td>8</td>
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<tr>
<td>CD38 molecule</td>
<td>8</td>
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<tr>
<td>epidermal growth factor receptor</td>
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<td>MAGE family member A4</td>
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<td>ANTXR cell adhesion molecule 1</td>
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<tr>
<td>interleukin 13 receptor subunit alpha 2</td>
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<tr>
<td>interleukin 3 receptor subunit alpha</td>
<td>7</td>
</tr>
<tr>
<td>KRAS proto-oncogene, GTPase</td>
<td>7</td>
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</tbody>
</table>

Source: Pharmaprojects| Informa, April 2022

<table>
<thead>
<tr>
<th>Non-oncology targets</th>
<th>Number of therapies</th>
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</thead>
<tbody>
<tr>
<td>coagulation factor VIII</td>
<td>12</td>
</tr>
<tr>
<td>coagulation factor IX</td>
<td>9</td>
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<tr>
<td>dystrophin</td>
<td>9</td>
</tr>
<tr>
<td>vascular endothelial growth factor A</td>
<td>9</td>
</tr>
<tr>
<td>glucosylceramidase beta</td>
<td>8</td>
</tr>
<tr>
<td>ATP binding cassette subfamily A member 4</td>
<td>7</td>
</tr>
<tr>
<td>CF transmembrane conductance regulator</td>
<td>7</td>
</tr>
<tr>
<td>C9orf72-5MCR8 complex subunit</td>
<td>7</td>
</tr>
<tr>
<td>collagen type VII alpha 1 chain</td>
<td>7</td>
</tr>
<tr>
<td>hemoglobin subunit beta</td>
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<tr>
<td>huntingtin</td>
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</tr>
<tr>
<td>synuclein alpha</td>
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<tr>
<td>TNF receptor superfamily member 17</td>
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<tr>
<td>apolipoprotein E</td>
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<tr>
<td>C-C motif chemokine receptor 5</td>
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<tr>
<td>galactosidase alpha</td>
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</tr>
<tr>
<td>gap junction protein beta 2</td>
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<tr>
<td>glucosidase alpha, acid</td>
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</tr>
<tr>
<td>granulin precursor</td>
<td>7</td>
</tr>
<tr>
<td>microtubule associated protein tau</td>
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<tr>
<td>N-acetyl-alpha-glucosaminidase</td>
<td>7</td>
</tr>
<tr>
<td>serpin family A member 1</td>
<td>7</td>
</tr>
<tr>
<td>superoxide dismutase 1</td>
<td>7</td>
</tr>
<tr>
<td>ubiquitin protein ligase E3A</td>
<td>7</td>
</tr>
<tr>
<td>UL56, cytomegalovirus</td>
<td>7</td>
</tr>
</tbody>
</table>

Source: Pharmaprojects| Informa, April 2022
Gene therapy clinical trial activity

- As in Q4 2021, 55 trials were initiated in Q1 2022 for gene therapies.
- The trend of an increasing proportion of gene therapy trials for non-oncology indications has not continued into 2022 so far, with 25% of the newly initiated trials in Q1 2022 being for non-oncology diseases compared to 35% in Q4 2021.

Source: Trialtrove | Informa, April 2022
Non-genetically modified cell therapy pipeline
Non-genetically modified cell therapy pipeline: Most common therapeutic areas targeted

Of the cell therapies in development (preclinical through pre-registration):

- Oncology and rare diseases continue to be the top areas of non-genetically modified cell therapy development
- Of the non-genetically modified cell therapies in preclinical to pre-registration stages for rare diseases, 63% are in development for non-oncology rare diseases, a decrease of 11% compared to Q4 2021

*figures based on indications in pipeline development only for each therapy

Source: Pharmaprojects| Informa, April 2022

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticancer</td>
<td>290</td>
</tr>
<tr>
<td>Rare Diseases</td>
<td>257</td>
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<tr>
<td>Alimentary/Metabolic</td>
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<tr>
<td>Musculoskeletal</td>
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<tr>
<td>Neurological</td>
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<tr>
<td>Cardiovascular</td>
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<td>Immunological</td>
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<tr>
<td>Respiratory</td>
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<tr>
<td>Miscellaneous</td>
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<tr>
<td>Sensory</td>
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<tr>
<td>Dermatological</td>
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<tr>
<td>Genitourinary (including sex hormones)</td>
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<tr>
<td>NA/Unspecified</td>
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<tr>
<td>Anti-Infective</td>
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<tr>
<td>Blood and Clotting</td>
<td>25</td>
</tr>
<tr>
<td>Hormonal (excluding sex hormones)</td>
<td>4</td>
</tr>
</tbody>
</table>
Non-genetically modified cell therapy pipeline: Most common diseases targeted

Of the diseases for which indications are specified, the top three indications remain the same as in Q4 2021:

1. Respiratory distress syndrome
2. COVID-19 complications
3. Osteo arthritis

*figures based on indications in pipeline development only for each therapy

Source: Pharmaprojects| Informa, April 2022
Non-genetically modified cell therapy pipeline: Most common rare diseases targeted

Of the cell therapies in development (preclinical through pre-registration) for rare diseases:

- The top three oncology indications are acute myelogenous leukemia, myeloma, and ovarian cancer
- The top three non-oncology indications remain to be acute respiratory distress syndrome, graft-versus-host disease, and amyotrophic lateral sclerosis

*Figures based on indications in pipeline development only for each therapy*
Non-genetically modified cell therapy trial activity

- 32 trials were initiated for non-genetically modified cell therapies in Q1 2022, and of these 69% are for non-oncology indications.

Source: Trialtrove | Informa, April 2022
RNA therapy pipeline
RNA therapy pipeline: Most common modalities

- Q1 2022 has continued the trends established in 2021 of an overall increase in messenger RNA and RNA interference therapies in pipeline (preclinical to pre-registration) development, rising to 278 and 245, respectively.
RNAi, mRNA, and antisense oligonucleotides: Preclinical vs. clinical

- Preclinical development continues to dominate RNAi, mRNA, and antisense therapeutic development, representing 80%, 76%, and 64% of development respectively.
RNA therapies: Most commonly targeted therapeutic areas

Of the 823 RNA therapies currently in the pipeline (from preclinical through pre-registration):

- Rare diseases remain the top therapeutic area being targeted by RNA therapies, while anticancer therapies have regained their position as the second most common RNA therapy type, overtaking anti-infective therapies.
- As found in Q4 2021, of all the RNA therapies in preclinical to pre-registration development for rare diseases, 80% are in development for non-oncology rare diseases.

*Source: Pharmaprojects| Informa, April 2022*  
*Figures based on indications in pipeline development only for each therapy*
RNA therapies: Most common rare diseases targeted

Of the RNA therapies currently in the pipeline (from preclinical through pre-registration):

- Top specified rare oncology indications are pancreatic, liver, and ovarian cancer
- For non-oncology rare diseases, Duchenne’s muscular dystrophy, amyotrophic lateral sclerosis, and Huntington’s disease are the top most commonly targeted indications

*figures based on indications in pipeline development only for each therapy
RNA therapy pipeline: Clinical trial activity

- 44 RNA trials were initiated in Q1 2022, compared to 49 in Q4 2021, 93% of which were for oncology indications

Source: Trialtrove | Informa, April 2022
Alliance, acquisition, and financing in gene, cell, & RNA therapy

• In Q1 2022, a total of 123 deals were signed, a 15% decrease in volume from Q4 2021
• Q1 2022 also featured the lowest quarter total within the last year, and represented a 26% decrease from the 167 deals done in the opening quarter of 2021
• Acquisition and alliance volume quarter by quarter remains flat, while financings continue to trend down

Total number of deals by type, most recent five quarters

Source: Biomedtracker | Informa, April 2022

*Financings include public financings (IPOs and follow-ons) plus privately raised funding through venture rounds, debt offerings, or private investment in public equity
Q1 2022 acquisitions in gene, cell, & RNA therapy

- Acquisitions were the only deal type to see an increase in Q1 2022, where there were 8 transactions done compared with 6 in Q4 2021
- In the largest takeover, Intellia paid $200M to acquire Rewrite Therapeutics, which develops DNA writing technologies for genome editing
- Recipharm was responsible for 2 of the 8 acquisitions of the quarter, buying CDMOs GenIbet and Vibalogics

<table>
<thead>
<tr>
<th>Deal Date</th>
<th>Deal Title</th>
<th>Potential Deal Value (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/07/2022</td>
<td>Kriya Expands Gene Therapy Pipeline and Establishes Rare Disease Therapeutic Area Division With the Acquisition of Warden Bio</td>
<td>Undisclosed</td>
</tr>
<tr>
<td>01/10/2022</td>
<td>Castle Creek Biosciences Acquires Novavita Thera to Expand Innovative Cell and Gene Therapy Platform</td>
<td>Undisclosed</td>
</tr>
<tr>
<td>01/18/2022</td>
<td>ProKidney to Become Publicly Traded via Business Combination with Social Capital Suvretta Holdings Corp. III</td>
<td>Undisclosed</td>
</tr>
<tr>
<td>01/28/2022</td>
<td>Oxford Biomedica Pays $175M for Homology Medicine’s 80% Stake in AAV Manufacturing Business Oxford Biomedica Solutions LLC</td>
<td>175,000,000</td>
</tr>
<tr>
<td>02/01/2022</td>
<td>Polyplus Acquires Plasmid DNA Vector Company e-Zyvec</td>
<td>Undisclosed</td>
</tr>
<tr>
<td>02/01/2022</td>
<td>Recipharm Buys GenIbet, a Portuguese CDMO</td>
<td>Undisclosed</td>
</tr>
<tr>
<td>02/03/2022</td>
<td>Intellia Therapeutics Acquires Rewrite Therapeutics</td>
<td>200,000,000</td>
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<tr>
<td>02/18/2022</td>
<td>Recipharm Buys CDMO Vibalogics</td>
<td>Undisclosed</td>
</tr>
</tbody>
</table>

Source: Biomedtracker | Informa, April 2022
Start-up funding for gene, cell, & RNA therapy companies
Start-up financing for gene, cell, & RNA therapy companies

- 15 companies raised seed or Series A financing in Q1 2022, together totaling $507.8M; the number of companies and aggregate raised was virtually flat compared with Q4 2021, when 15 companies brought in $510.3M
- Q1 2022 was stronger than the opening quarter of 2021, when 13 companies amassed $479.8M in seed or Series A financing
- Cellino Biotech, an autologous and allogeneic cell manufacturing company, raised the largest financing with an $80M Series A round
- Note: The Q1 2022 totals do not include Affini-T Therapeutics’ $175M financing, which the CEO said combined seed, Series A, and Series B cash

Source: Biomedtracker| Informa, April 2022; Scrip| Informa, March 2022
## Q1 2022 start-up financing for gene, cell, & RNA therapy companies (1/2)

<table>
<thead>
<tr>
<th>Deal Date</th>
<th>Deal Title</th>
<th>Modality Type</th>
<th>Company Location</th>
<th>Academic Source</th>
<th>Potential Deal Value (USD, $M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/04/2022</td>
<td>Ray Therapeutics Closes $6M Seed Financing</td>
<td>Gene therapy (optogenetics)</td>
<td>United States, California, San Diego</td>
<td>Undisclosed</td>
<td>6</td>
</tr>
<tr>
<td>01/06/2022</td>
<td>ONK Therapeutics Raises $21.5M Series A Financing</td>
<td>Cell therapy (NK cells)</td>
<td>Ireland, Galway</td>
<td>National University of Ireland, Galway, and Australia's Walter and Eliza Hall Institute of Medical Research</td>
<td>21.5</td>
</tr>
<tr>
<td>01/19/2022</td>
<td>Ceptur Therapeutics Launches with $75M Series A Financing to Advance RNA Therapeutics Based on Proprietary U1 Adapter Technology</td>
<td>Oligonucleotides</td>
<td>United States, New Jersey, Hillsborough</td>
<td>Rafal Goraczniak (inventor; currently Ceptur's director of platform development)</td>
<td>75</td>
</tr>
<tr>
<td>01/19/2022</td>
<td>64x Bio Closes $55M Series A Round to Fund Expansion of VectorSelect Platform</td>
<td>Cell line engineering for gene therapies</td>
<td>United States, California, San Francisco</td>
<td>Harvard Department of Genetics</td>
<td>55</td>
</tr>
<tr>
<td>01/25/2022</td>
<td>Cellino Biotech Raises $80M Series A Financing</td>
<td>Cell therapy (manufacturing, autologous and allogeneic)</td>
<td>United States, Massachusetts, Cambridge</td>
<td>Harvard University</td>
<td>80</td>
</tr>
<tr>
<td>02/10/2022</td>
<td>Indapta Therapeutics Raises $50M in Series A Financing</td>
<td>Cell therapy (NK cells)</td>
<td>United States, California, San Francisco</td>
<td>University of California, Davis</td>
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</tr>
<tr>
<td>02/10/2022</td>
<td>Ucello Therapeutics Completes $25M Series A Financing</td>
<td>Cell therapy (CAR-T)</td>
<td>China</td>
<td>Undisclosed</td>
<td>25</td>
</tr>
<tr>
<td>02/16/2022</td>
<td>SpliceBio Raises $56.7M in an Oversubscribed Series A Financing</td>
<td>Gene therapy (improved delivery using protein splicing platform)</td>
<td>Spain, Barcelona</td>
<td>Muir Lab at Princeton University</td>
<td>56.8</td>
</tr>
<tr>
<td>02/23/2022</td>
<td>hC Bioscience Closes $24M Series A Financing</td>
<td>tRNA therapeutics</td>
<td>United States, Massachusetts, Cambridge</td>
<td>University of Iowa</td>
<td>24</td>
</tr>
</tbody>
</table>

Source: Biomedtracker | Informa, April 2022
<table>
<thead>
<tr>
<th>Deal Date</th>
<th>Deal Title</th>
<th>Modality Type</th>
<th>Company Location</th>
<th>Academic Source</th>
<th>Potential Deal Value (USD, $M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>03/01/2022</td>
<td>NextRNA Secures $46.8M in a Series A Round</td>
<td>Small molecules that address protein interactions with non-coding RNA</td>
<td>United States, Massachusetts, Cambridge</td>
<td>Dana-Farber Cancer Institute</td>
<td>46.8</td>
</tr>
<tr>
<td>03/01/2022</td>
<td>NextRNA Launches with $9.3M in Seed Financing</td>
<td>Small molecules that address protein interactions with non-coding RNA</td>
<td>United States, Massachusetts, Cambridge</td>
<td>Dana-Farber Cancer Institute</td>
<td>9.3</td>
</tr>
<tr>
<td>03/17/2022</td>
<td>Zhongbo Ruikang Raises up to USD15.7 Million in Series A Financing</td>
<td>Cell and gene therapy tools and services</td>
<td>China, Beijing</td>
<td>Undisclosed</td>
<td>15.7</td>
</tr>
<tr>
<td>03/20/2022</td>
<td>CRISP-HR Therapeutics Raises Funds through Seed Financing</td>
<td>CRISPR gene editing</td>
<td>United States, California, San Carlos</td>
<td>Co-founders from NYU and Georgia Tech</td>
<td>Undisclosed</td>
</tr>
<tr>
<td>03/21/2022</td>
<td>Suzhou Qiheshengke Biotech Raises USD15.7 Million in Seed Financing</td>
<td>Gene editing</td>
<td>China, Suzhou</td>
<td>Undisclosed</td>
<td>15.7</td>
</tr>
<tr>
<td>03/29/2022</td>
<td>RNAimmune Raises $27M Series A Financing</td>
<td>mRNA vaccines and therapeutics</td>
<td>United States, Maryland, Gaithersburg</td>
<td>n/a - subsidiary of Sirnaomics</td>
<td>27</td>
</tr>
</tbody>
</table>

Source: Biomedtracker | Informa, April 2022
# Notable Q1 2022 start-up gene, cell, & RNA therapy companies

<table>
<thead>
<tr>
<th>Company details</th>
<th>Academic source</th>
<th>Financing type/amount raised</th>
<th>Lead investor(s)</th>
<th>Therapy areas of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large-scale production of personalized cell therapies: automated cell reprogramming, expansion, and differentiation in a closed cassette format</td>
<td>Harvard University</td>
<td>Series A/$80M</td>
<td>Leaps by Bayer, 8VC, and Humboldt Fund</td>
<td>Undisclosed</td>
</tr>
<tr>
<td>U1 adapter therapeutics (bivalent oligonucleotides) that control gene expression at the pre-mRNA level</td>
<td>Rafal Goraczniak (inventor; currently Ceptur’s director of platform development)</td>
<td>Series A/$75M</td>
<td>venBio Partners and Qiming Venture Partners USA</td>
<td>Oncology, CNS, nephrology, and immunology</td>
</tr>
<tr>
<td>Protein splicing platform (next-generation engineered split inteins) for development of gene therapies</td>
<td>Muir Lab at Princeton University</td>
<td>Series A/$56.8M</td>
<td>UCB Ventures and Ysios Capital</td>
<td>Ophthalmology</td>
</tr>
</tbody>
</table>

Source: Biomedtracker | Informa, April 2022
Upcoming catalysts
## Upcoming Catalysts

Below are noteworthy catalysts (forward looking events) expected in Q2 2022

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Generic Name</th>
<th>Disease</th>
<th>Catalyst</th>
<th>Catalyst Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kymriah</td>
<td>tisagenlecleucel-t</td>
<td>Indolent Non-Hodgkin’s Lymphoma (Including Follicular Lymphoma) - NHL</td>
<td>PDUFA for sBLA - First Review</td>
<td>27 Apr 2022 – 27 Apr 2022</td>
</tr>
<tr>
<td>PTC-AADC</td>
<td>eladocagene exuparvovec</td>
<td>Neurology - Other</td>
<td>CHMP Opinion</td>
<td>1 Apr 2022 – 30 Apr 2022</td>
</tr>
<tr>
<td>Lantidra</td>
<td>Allogeneic Islets of Langerhans</td>
<td>Diabetes Mellitus, Type I</td>
<td>PDUFA for BLA - First Review</td>
<td>7 Mar 2022 – 31 May 2022</td>
</tr>
<tr>
<td>Zynteglo</td>
<td>betibeglogene autotemcel</td>
<td>Thalassemia</td>
<td>FDA Advisory Panel Brief</td>
<td>7 Jun 2022 – 8 Jun 2022</td>
</tr>
<tr>
<td>Zynteglo</td>
<td>betibeglogene autotemcel</td>
<td>Thalassemia</td>
<td>FDA Advisory Panel Meeting</td>
<td>9 Jun 2022 – 10 Jun 2022</td>
</tr>
<tr>
<td>Lenti-D</td>
<td>elivaldogene autotemcel</td>
<td>Adrenoleukodystrophy</td>
<td>FDA Advisory Panel Meeting</td>
<td>9 Jun 2022 – 10 Jun 2022</td>
</tr>
<tr>
<td>Breyanzi</td>
<td>lisocabtagene maraleucel</td>
<td>Diffuse Large B-Cell Lymphoma (DLBCL) - NHL</td>
<td>PDUFA for sBLA - 2L LBCL</td>
<td>24 Jun 2022 – 24 Jun 2022</td>
</tr>
<tr>
<td>Roctavian</td>
<td>valoctocogene roxaparvovec</td>
<td>Hemophilia A</td>
<td>CHMP Opinion</td>
<td>9 Jan 2022 – 30 Jun 2022</td>
</tr>
<tr>
<td>Yescarta</td>
<td>axicabtagene ciloleucel</td>
<td>Diffuse Large B-Cell Lymphoma (DLBCL) - NHL</td>
<td>Supplemental CHMP Opinion</td>
<td>1 May 2022 – 31 Oct 2022</td>
</tr>
<tr>
<td>Oxlimo</td>
<td>lumasiran</td>
<td>Hyperoxaluria</td>
<td>CHMP Supplemental Opinion</td>
<td>1 May 2022 – 31 Oct 2022</td>
</tr>
<tr>
<td>vutrisiran</td>
<td>vutrisiran</td>
<td>Hereditary Transthyretin (hATTR) Amyloidosis With Polyneuropathy (Familial Amyloid Polyneuropathy)</td>
<td>CHMP Opinion</td>
<td>1 Jun 2022 – 31 Dec 2022</td>
</tr>
</tbody>
</table>

Source: Biomedtracker | Informa, April 2022
Appendix

Methodology, sources, & glossary of key terms
Methodology: Sources and scope of therapies

Sources for all data come from Informa Pharma Intelligence

Pipeline and trial data
- Data derived from Citeline (Pharmaprojects and Trialtrove)
- Therapeutic classes included in report categorizations:
  - Gene therapies: Gene therapy; cellular therapy, chimeric antigen receptor; cellular therapy, T cell receptor; lytic virus
  - Cell therapies: Cellular therapy, other; cellular therapy, stem cell; cellular therapy, tumor-infiltrating lymphocyte
  - RNA therapies: Messenger RNA; oligonucleotide, non-antisense, non-RNAi; RNA interference; antisense therapy

Deal, financing, and catalyst data
- Data derived from Biomedtracker
- The following industry categorizations of deals are included: Gene therapy, cell therapy; antisense, oligonucleotides
# Glossary of Key Terms

## Therapy Type Definitions

**Gene therapy** is the use of genetic material to treat or prevent disease. For the purpose of this report, the following terms shall mean the following:

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gene therapy</strong></td>
<td>Therapies containing an active ingredient synthesized following vector-mediated introduction of a genetic sequence into target cells <em>in</em>-<em>vivo</em> or *ex-*vivo. Used to replace defective or missing genes (e.g. cystic fibrosis) as well as to introduce broadly acting genetic sequences for the treatment of multifactorial diseases (e.g. cancer). Direct administration of oligonucleotides without using vectors is covered separately in the antisense therapy class; RNA interference class; or oligonucleotide, non-antisense, non-RNAi class. Platform technologies for gene delivery are covered separately in the gene delivery vector class.</td>
</tr>
<tr>
<td><strong>Cellular therapy, chimeric antigen receptor</strong> <em>Falls under gene therapy in this report</em></td>
<td>Cellular therapy consisting of T cells that have been modified to express a chimeric antigen receptor (CAR) – this is a cell surface receptor that gives the T cells the ability to target a specific protein and fight the targeted cells.</td>
</tr>
<tr>
<td><strong>Cellular therapy, T cell receptor</strong> <em>Falls under gene therapy in this report</em></td>
<td>Cellular therapies whereby natural T-cells collected for the patient, are engineered to express artificial receptors (usually through viral transfections) that would target specific intracellular antigens (as peptides bound to proteins encoded by the major histocompatibility complex, MHC).</td>
</tr>
<tr>
<td><strong>Lytic virus</strong> <em>Falls under gene therapy in this report</em></td>
<td>Therapies which have a replication-competent virus, that lyse pathogenic cells directly. These are normally genetically modified to render them harmless to normal tissues. Examples include oncolytic viruses which specifically attack cancer cells.</td>
</tr>
</tbody>
</table>
# Glossary of Key Terms

**Therapy type definitions, cont.**

**Cell therapy** includes the following therapeutic classes:

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cellular therapy, stem cell</strong></td>
<td>Regenerative therapy which promotes the repair response of injured tissue using stem cells (cells from which all other specialized cells would originate).</td>
</tr>
<tr>
<td><strong>Cellular therapy, tumor infiltrating lymphocyte</strong></td>
<td>Adoptive cellular transfer of tumor resident T cells from tumor material, their expansion <em>ex vivo</em>, and transfer back into the same patient after a lymphodepleting preparative regimen.</td>
</tr>
<tr>
<td><strong>Cellular therapy, other</strong></td>
<td>Cellular therapies that do not fall under the categories of cellular therapy, stem cell; cellular therapy, CAR; cellular therapy, TIL; cellular therapy, TCR; or the specific cellular therapy are unspecified.</td>
</tr>
</tbody>
</table>
**Glossary of Key Terms**

**Therapy type definitions, cont.**

**RNA therapy** includes the following therapeutic classes:

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Messenger RNA</strong></td>
<td>Therapies that carry the desired mRNA code to overcome genetic mutations. The mRNA sequence will replace the defective mRNA in a patient and starts producing the desired protein.</td>
</tr>
<tr>
<td><strong>Oligonucleotide, non-antisense, non-RNAi</strong></td>
<td>Synthetic therapeutic oligonucleotides which operate by a mechanism other than antisense or RNA interference (RNAi). This includes ribozymes, aptamers, decoys, CpGs, and mismatched and immunostimulant oligonucleotides. Sequences delivered using vectors (gene therapy) are covered separately in “gene therapy.” Antisense and RNAi oligonucleotides are covered separately in “antisense therapy” and “RNA interference,” respectively.</td>
</tr>
<tr>
<td><strong>RNA interference</strong></td>
<td>Includes products which act therapeutically via an RNA interference (RNAi) mechanism, including small interfering RNAs (siRNAs). These may be synthetic oligonucleotides, or RNAi sequences may be expressed from a vector as a form of gene therapy (see “gene therapy” therapeutic class). In vivo, these sequences block the expression of a specific protein by forming an RNA-induced silencing complex, which then specifically binds to and degrades a complementary mRNA encoding the target protein. The use of RNAi purely as a drug discovery tool (e.g., in transgenic animal model production or in target validation) is not covered in this section.</td>
</tr>
<tr>
<td><strong>Antisense therapy</strong></td>
<td>Antisense compounds under development as potential therapeutics. These may be synthetic oligonucleotides, or antisense RNA may be expressed from a vector as a form of gene therapy. They may prevent the expression of a specific protein <em>in vivo</em> by binding to and inhibiting the action of mRNA, since they have a specific oligonucleotide sequence which is complementary to the DNA or RNA sequence which codes for the protein.</td>
</tr>
</tbody>
</table>
### Glossary of Key Terms

#### Development status definitions

<table>
<thead>
<tr>
<th>Status</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pipeline</td>
<td>Drugs that are in active development</td>
</tr>
<tr>
<td>Preclinical</td>
<td>Not yet tested in humans</td>
</tr>
<tr>
<td>Phase I</td>
<td>Early trials, usually in volunteers, safety, PK, PD</td>
</tr>
<tr>
<td>Phase II</td>
<td>First efficacy trials in small numbers of patients</td>
</tr>
<tr>
<td>Phase III</td>
<td>Large scale trials for registrational data</td>
</tr>
<tr>
<td>Pre-registration</td>
<td>Filing for approval made to regulatory authorities</td>
</tr>
<tr>
<td>Approved</td>
<td>Approval from relevant regulatory authorities for human use</td>
</tr>
</tbody>
</table>

#### Deal type categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alliances</td>
<td>Co-marketing, co-promotion, disease management, joint venture, manufacturing or supply, marketing-licensing, product or technology swap, product purchase, R+D and marketing-licensing, reverse licensing, trial collaborations</td>
</tr>
<tr>
<td>Financing</td>
<td>Convertible debt, FOPO, IPO, nonconvertible debt, financing/other, private investment in public equity, private placement, royalty sale, special-purpose financing vehicle, spin-off</td>
</tr>
<tr>
<td>Acquisitions</td>
<td>Buy-out, divestiture, spin-out, full acquisition, partial acquisition, reverse acquisition</td>
</tr>
</tbody>
</table>

#### Unspecified indications

<table>
<thead>
<tr>
<th>Indication</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer, unspecified</td>
<td>Indications for which the specific tumor type is not specified</td>
</tr>
<tr>
<td>Cancer, hematological, unspecified</td>
<td>Indications for which the specific hematological cancer is not specified</td>
</tr>
<tr>
<td>Cancer, solid, unspecified</td>
<td>Indications for which the specific solid tumor is not specified</td>
</tr>
</tbody>
</table>
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