EDISON

Cell and gene therapies

Ambitious vision or the real deal?

Edison themes

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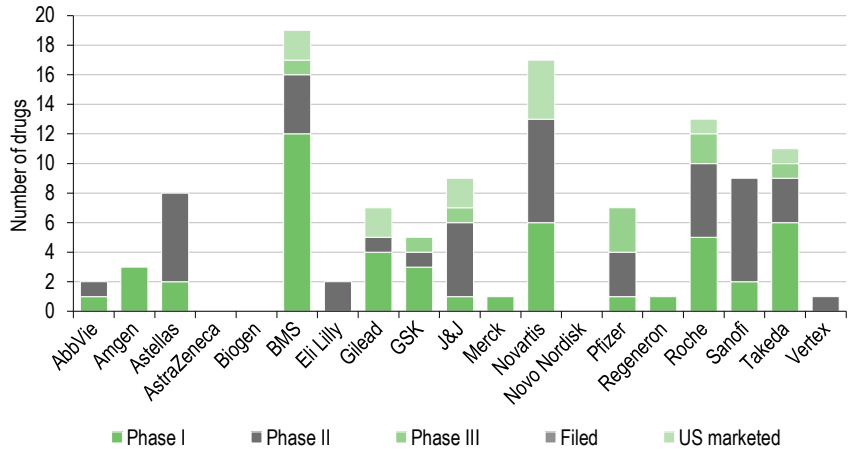
It is fair to say that cell and gene therapies (CGTs) have not walked an easy road, from reaching the peak of excitement in the 1990s to descent into a period of disillusionment following a spate of safety red flags in the technologies' early clinical days. However, intensified clinical research and investment has, to some extent, helped certain CGTs weather the storm in bringing the first generation of these new drug modalities to market. Yet, with elevated pricing, manufacturing complexities and the limited disease scope that current CGT treatments can target, they are by no means, to date, therapies for the masses. These challenges can only be addressed through continued innovation, which we believe is housed in biotech companies. Ultimately, it will be the most robust science that unlocks the true potential and opportunity that CGTs possess.

Separating the hype from the science

CGTs have undoubtedly topped the list of clinical buzzwords over the last 20 years, but much hype coupled with very few wins left many questioning whether CGTs were nothing more than a therapeutic pipedream. With innovative advancements in gene-editing strategies, delivery technologies and an increasing number of biotechs focused on CGT development, the 2010s finally gave way to the first wave of CGT clinical successes.

Such approvals certainly indicate that the field is heading in the right direction; however, it will be important to not get caught up in a second CGT hype cycle, as concerns over toxicity and treatment durability continue to linger. For CGT development to make further strides, it must be rooted in companies with a solid scientific foundation aimed at making treatments more effective, safer and affordable. Indeed, some big pharma players have firmly backed CGT technologies with substantial financial investment in the form of biotech deals, stockpiling their CGT pipelines in anticipation of delivering the next blockbuster (see Exhibit 1).

Exhibit 1: Big pharma CGT pipelines



Source: Evaluate Pharma, Edison Investment Research

Advancements in cell and gene therapy continue to rely on highly focused and specialised technology developed by smaller and nimbler biotech companies. Mechanisms will continue to evolve and fuel advancements in targeted treatments and therapies with more broad-based offerings within large pharma portfolios.

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As one of the largest issuer-sponsored research firms, we are known for our bottom-up work on individual stocks. However, our thinking does not stop at the company level. Through our regular dialogue with management teams and investors, we consider the broad themes related to the companies we follow. Edison themes aims to identify the big issues likely to shape company strategy and portfolios in the years ahead.

Analysts

Soo Romanoff +44 (020) 3077 5700

Dr Adam McCarter +44 (020) 3077 5700

healthcare@edisongroup.com

Companies mentioned in this report (Edison clients in bold)

4D Molecular Therapeutics (FDMT: NASDAQ)
Alaunos Therapeutics (TCRT: NASDAQ)
Allogene Therapeutics (ALLO: NASDAQ)
BioMarin (BMRN: NASDAQ)
Bluebird bio (BLUE: NASDAQ)
Bristol Myers Squibb (BMY: NYSE)
Cellectis (CLLS: NASDAQ)
Century Therapeutics (IPSC: NASDAQ)
Gilead (GILD: NASDAQ)
ImmixBio (IMMX: NASDAQ)
Johnson & Johnson (JNJ: NYSE)
Marker Therapeutics (MRKR: NASDAQ)
Novartis (NVS: NYSE)
Poseida Therapeutics (PSTX: NASDAQ)
Precision BioSciences (DTIL: NASDAQ)
Sarepta Therapeutics (SRPT: NASDAQ)
Roche Holding (RO: SIX)
Takeda (TAK: NYSE)
TCR2 Therapeutics (TCRR: NASDAQ)

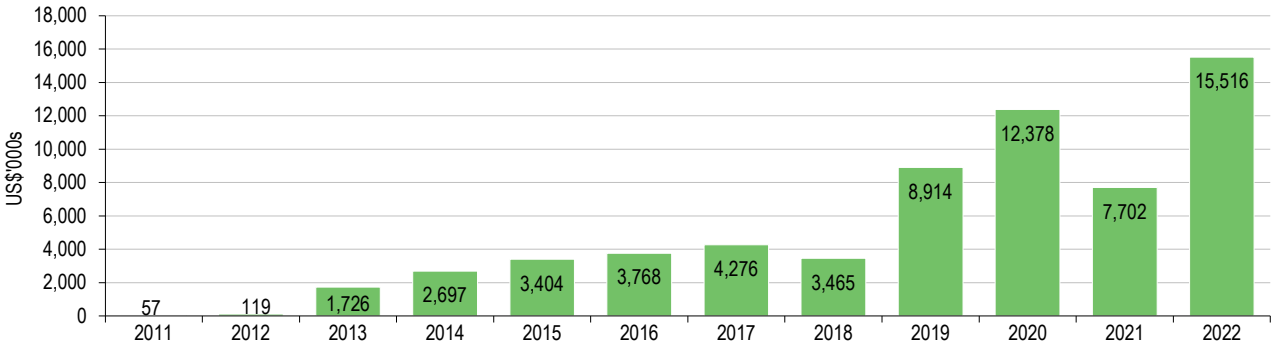
Those who paid up lead the way

While some steadfast sceptics will take the stance that CGTs are simply overhyped, this is by no means a universal sentiment. It is certainly not a view shared across big pharma peers, with many having and continuing to show a longstanding interest in CGTs, shoring up their commitment with some of the industry's most lucrative transactions. The most notable deals include Bristol Myers Squibb's (BMS's) mammoth US$74bn takeover of Celgene, which included the company's CGT portfolio, leading to the launch of BMS's first gene-modified CAR-T cell therapy, Breyanzi, in February 2021. Roche's US$4.8bn acquisition of Spark Therapeutics also brought about a first in 2017: the approval of Luxturna as the first gene therapy to treat an inherited genetic condition.

Despite such prominent deals, CGTs, with their safety track record and potentially untenable economic profiles, are still considered a high-risk space in the context of the overall biotech market. Given the current macroeconomic conditions, M&A activity has seen an industry-wide slowdown and we anticipate that potential big pharma acquirers will be more likely to wait for solid clinical evidence to appear from a biotech's pipeline before pursuing a CGT acquisition.

However, CGT transactions have not just taken the form of company acquisitions; licensing deal values have shown an increasing trend in recent years (Exhibit 2). Many biopharmas are still dipping into their pockets and 2022 has, to date, been one of the most prominent years yet for licensing activity in the CGT space.

Exhibit 2: CGT licensing deal values



Source: Evaluate Pharma, Edison Investment Research. Note: 2022 figure as of 15 December 2022.

The 2022 figure was propped up by Roche's deal with Poseida Therapeutics, worth up to c US$6bn in total payments and milestones (excluding sales royalties), to develop donor-derived ('off-the-shelf') CAR-T cell therapies for the treatment of haematologic malignancies. BMS's deal with Century Therapeutics, again investigating off-the-shelf immune cell therapies (CAR-T, NK cells) in blood cancers and worth up to c US$3bn in payments and milestones (excluding royalties), also represented one of the more significant CGT transactions in 2022. We see these larger deal values as positive indicators that the CGT segment is beginning to mature and expect licensing to form the bulk of ongoing CGT transaction activity as the market continues to develop and further CGT clinical successes are realised.

CGTs: Take care to differentiate

While the term CGTs is often used as a collective, it is important to understand that it encompasses multiple different technologies. Even among those more literate in biotech jargon, the terms 'cell therapy' and 'gene therapy' are often used interchangeably and, in some cases, incorrectly.

Understanding the differences is critical as each technology has applications across different markets and disease areas and is at varying levels of maturity. While there may be some degree of crossover, we believe CGTs can broadly be split into three main categories: cell therapy, gene-modified cell therapy and gene therapy (Exhibit 3).

Exhibit 3: Cell and gene therapies overview

Technology	Estimated 2028 global product sales*	How it works	Advantages	Disadvantages	Selected FDA approved therapies
Cell therapy	US$10.2bn	Can be more commonly thought of in the context of regenerative medicine using a patient's own (autologous) or donor (allogenic) cells, often stem cells, to repair or restore damaged tissues or organs.	■ Can help avoid surgical intervention and associated risks ■ Potential to treat a variety of conditions including cancer, autoimmune, cardiovascular and neurodegenerative diseases ■ May be combined with other emerging technologies (such as CAR-T) in the design of new treatments to tackle disease	■ Donor-derived therapies are primarily limited to bone marrow transplants to treat patients with blood disorders such as haematological cancers ■ Personalised (autologous) treatments result in time-consuming manufacturing ■ Long-term safety profiles still unknown with unproven cell therapies carrying cancer risk	■ MACI (Vericel) ■ Epicel (Vericel) ■ Rethymic (Enzyvant)
Gene-modified cell therapy	US$23.8bn	Specific cells, usually immune system T cells, are removed from patients, genetically modified and re-administered, allowing the modified immune cells to target and fight diseased cells. Most advanced within the category are CAR T-cell therapies for anti-cancer treatment.	■ Durable responses and short treatment time period where responses can be achieved after single dose ■ May act as an alternative treatment to aggressive chemotherapy ■ Improve immunological memory that may provide continuous surveillance against cancer cells	■ Currently limited to non-solid tumours (haematological malignancies) ■ No approved 'off-the-shelf' donor-derived (allogenic) cell therapies ■ Personalised treatments result in time-consuming and costly manufacturing	■ Kymriah (Novartis) ■ Breyanzi (Bristol Myers) ■ Yescarta (Gilead)
Gene therapy	US$19.1bn	Where a healthy copy of a gene is delivered to cells inside the body to replace a gene that is missing or damaged (mutated) causing disease. Genes are delivered to cells through carriers called vectors, the most common being viral vectors. Gene therapies have currently found use for the treatment of rarer diseases.	■ May act as a one-off treatment for inherited disorders ■ Potential to treat a variety of conditions ■ One-time treatment can result in improved patient compliance	■ Oncologic safety concerns with certain technologies ■ High prices bring challenges with reimbursement ■ Have been associated with liver toxicity	■ Skysona (Bluebird bio) ■ Zolgensma (Novartis) ■ Luxturna (Roche / Spark)

Source: Edison Investment Research, *Evaluate Pharma

Significant progress but not yet the finished articles

With notable clinical breakthroughs over the last five years that have brought drugs to market with blockbuster potential, gene-modified cell therapies and gene therapies have spent the most time in the spotlight recently. CAR-T therapies fall under the gene-modified banner and represent the most clinically advanced modality of this technology class. Following the approval of Novartis's Kymriah in 2017 as the first CAR-T cell therapy to treat cancer, a further five therapies have since made it through the clinic (Exhibit 4). While these CAR-T approvals provide important validation for the technology, existing treatments are highly personalised, requiring use of a patient's own immune T cells, resulting in costly and time-consuming production. Today, the focus of much clinical research is towards the development of donor-derived or 'off-the-shelf' CAR-T treatments that use immune cells from healthy donors to produce the CAR-T therapy. The development of donor-derived cell therapies would provide patients with more immediate access. To date, CAR-Ts have found a place as effective and durable treatments for haematological malignancies (blood cancers) but have yet to crack solid tumours. Again, this is the subject of many continued investigations, and breakthroughs could pave the way for the next generation of CAR-T therapies.

Exhibit 4: Selected FDA approved and upcoming reviews for gene-modified cell and gene therapies

Company	Drug	FDA approval	Approval indication	Drug type	Est. global sales 2028 US$**
Sarepta Therapeutics / Roche	SRP-9001	Review expected May 2023	Duchene muscular dystrophy	Gene therapy	2.2bn
BioMarin	Roctavian*	Review expected March 2023	Haemophilia A	Gene therapy	1.4bn
CSL Behring	Hemgenix	November 2022	Haemophilia B	Gene therapy	No estimates
Bluebird bio	Skysona	September 2022	Cerebral adrenoleukodystrophy (rare disease)	Gene therapy	21m
Bluebird bio	Zynteglo	August 2022	Beta thalassemia	Gene therapy	391m
Johnson & Johnson	Carvykti	February 2022	Multiple myeloma	Gene-modified cell therapy (CAR-T)	2.4bn
Bristol Myers / Bluebird bio	Abecma	March 2021	Multiple myeloma	Gene-modified cell therapy (CAR-T)	1.6bn
Bristol Myers	Breyanzi	February 2021	Large B-cell lymphoma	Gene-modified cell therapy (CAR-T)	1.6bn
Gilead / Kite	Tecartus	July 2020	Mantle cell lymphoma	Gene-modified cell therapy (CAR-T)	674m
Novartis	Zolgensma	May 2019	Spinal muscular atrophy	Gene therapy	2.1bn
Roche / Spark	Luxturna	December 2017	Retinal dystrophy	Gene therapy	136m
Gilead / Kite	Yescarta	October 2017	B-cell lymphoma	Gene-modified cell therapy (CAR-T)	2.2bn
Novartis	Kymriah	August 2017	B-cell precursor acute lymphoblastic leukaemia	Gene-modified cell therapy (CAR-T)	642m
Total gene therapy					6.2bn
Total gene-modified cell therapy					9.1bn

Source: Edison Investment Research, FDA cell and gene therapy approvals. Note: *Approved in EU. **According to Evaluate Pharma.

In contrast, gene therapies represent a fundamentally different type of drug from a mode of action, and from an economic and reputational perspective. Currently approved gene therapies have been developed to treat inherited diseases with a single defective gene and are intended to be administered to patients as one-time treatments, effectively fixing the underlying cause of the disease. On the face of it, a one-off administration to cure a life debilitating illness sounds like something of a miracle drug.

A major issue holding back the potential of gene therapy is that current technologies are simply not cost-effective. The extremely high costs of manufacturing and drug development lead to many of today's gene therapies carrying hefty price tags, typically in the range of US$2–3m per treatment, leaving many payers struggling to effectively justify coverage for such treatments. Additionally, while progress has undoubtedly been made, safety continues to cast a shadow, particularly on existing gene-delivery technologies (viral vectors), which continue to be linked to mutagenesis concerns and liver toxicity. The high price of gene therapies is likely to remain for the foreseeable future and, if they are to achieve market breakthroughs on a global scale, payers will need to adopt new ways of valuing one-time treatments compared to traditional treatments for chronic diseases. Technological advances will also be critical to shake the gene therapy safety concerns. These may come in the form of new gene-altering therapies, such as CRISPR, as well as the evolution of new gene-delivery platforms. For a more in-depth discussion on next-generation drug delivery, see our recent report, Drug delivery platforms: The unsung heroes of future drug discovery.

Biotechs the originators, but take lessons from Bluebird bio

A sentiment that continues to run through our healthcare investment theme reports is that while most new drugs have a big pharma label on the packaging, many discoveries can often be traced back to biotech companies. Edison healthcare client Immix Biopharma provides a first-hand example of a biotech looking to get its skin in the CAR-T game. The company recently made a strategic expansion with the in-licensing of NXC-201, a novel CAR-T therapy that has already shown high response rates in a Phase Ib/II study in multiple myeloma and amyloid light-chain (AL) amyloidosis. Additionally, the company believes NXC-201 holds potential to be the first and only out-patient CAR-T therapy.

In fact, just over half of FDA-approved gene and gene-modified cell therapies can trace their roots back to biotechs, with the remainder emerging from investigations at National Cancer Institute-designated cancer centres or academic institutions (Exhibit 5). Some of these CGTs have taken convoluted journeys to market through multiple acquisitions and licensing pathways.

Exhibit 5: Biotech originating cell and gene therapies

Company	Drug	Product source / developer	Transactions	Comments
Bristol Myers Squibb	Breyanzi	Juno Therapeutics	Acquisition	Juno acquired by Celgene for US$9bn, which was subsequently acquired by BMS for US$74bn
Novartis	Zolgensma	Avexis	Acquisition	Avexis acquired by Novartis for US$8.7bn
Johnson & Johnson	Carvytki	Legend Biotech / GenScript Biotech	In-licensed	J&J in-licensed from Legend Biotech
Bristol Myers Squibb	Abecma	Bluebird bio	Acquisition / in-licensed	Celgene in-licensed from Bluebird bio with Celgene subsequently acquired by BMS
Roche	Luxturna	Spark Therapeutics	Acquisition	Spark acquired by Roche for US$4.8bn
Bluebird bio	Skysona	Bluebird bio	N/A	Developed in-house
Bluebird bio	Zynteglo	Bluebird bio	N/A	Developed in-house

Source: Edison Investment Research

An interesting outlier from this trend is Bluebird bio, a United States-based gene therapy focused biotech that has taken the clinical and commercialisation path on its own. In August 2022, the company finally received FDA approval for Zynteglo, for treatment of the blood disorder beta thalassemia, and with a list price of US$2.8m it overtook Novartis's Zolgensma to become the world's most expensive drug. Bluebird subsequently broke its own record one month later with the approval of its second gene therapy product, Skysona, for the rare neurological disease cerebral adrenoleukodystrophy, clocking in at US$3m (this has since been overtaken by CSL Behring's Hemgenix). With the approvals, Bluebird's approved products hold the coveted titles of two of the world's most expensive drugs.

Yet with such a niche market Skysona is only projected to reach sales of US$13m by 2026 (Evaluate Pharma), while Zynteglo's numbers, considering its price, may also be considered moderate with forecasted sales of US$272m in 2026 (Evaluate Pharma). The company's inability to broker a deal with European payers may go some way towards explaining these figures, while cancer scares associated with Zynteglo may have restrained expectations of the drug. Despite the FDA approvals, investor confidence in Bluebird appears wavering, with the stock trading modestly at c US$5–10 per share in 2022 (having previously traded at c US$140 per share in early 2018) as the company voiced funding concerns and made staffing cuts earlier in the year, leading to many now viewing the company as a prime acquisition target. While the current macroeconomic conditions likely have not helped, Bluebird's stock has been on a steady downward trajectory since 2018, before the current biotech bear market. What the Skysona and Zynteglo FDA approvals have done is create a further impression of regulatory feasibility for new gene therapies, however we will have to wait to see whether the company's launches are commercial successes.

In our view, the Bluebird story perhaps best epitomises the elevated investor exuberance that can surround gene therapies. It highlights that, even if from a scientific perspective the technology is considered 'cutting edge' or 'next generational', if the health economics are not favourable or the clinical road has been rocky, regaining confidence and buy-in from stakeholders will be an uphill battle.

'Off-the-shelf' and tumour-targeting the next generation

Cell therapies are going to undoubtedly play an important role in the oncology treatment paradigm going forward. However, in our view, there are two critical milestones that would signify the next major advancements in the field: the development of 'off-the-shelf' (allogenic) therapies and proving the efficacy of cell therapies in solid tumours. There is no doubt that achieving such goals will be extremely challenging. Donor-derived allogenic therapies run a greater risk of triggering adverse

immune responses (graft versus host disease), while tumour cell heterogeneity (different cell types within a tumour), immunosuppressive tumour environments and inability to penetrate tumour masses represent some of the major barriers cell therapies face in solid tumour indications. However, many biotechs are committed to tackling these issues head on (Exhibit 6).

Exhibit 6: Selected cell therapies in biotech pipelines

Company	Drug	Indication	Technology	Notable points	Clinical status
Cellectis	UCART123	Acute myeloid leukaemia (AML)	Allogenic CAR-T	Targets CD123 expressed in c 80% of AML population so potential for broad AML sub-population application	Phase I
Allogene Therapeutics	ALLO-316	Renal cell carcinoma	Allogenic CAR-T	Achieved 33% response rate in CD70+ patients	Phase I (solid tumour)
Precision BioSciences	PBCAR0191	Relapsed or refractory (r/r) non-Hodgkin lymphoma and r/r B-cell acute lymphoblastic leukaemia.	Allogenic CAR-T	100% response rate achieved in autologous CAR-T relapsed patients	Phase I/II
Marker Therapeutics	MT-401	Acute myeloid leukaemia	Autologous / Allogenic non-genetically modified T-cell therapy	Multi-tumour antigen targeting. Use of non-genetically modified cells allows for manufacturing and cost efficiencies with potentially improved safety profiles	Phase II
TCR2 Therapeutics	TC-210 (Gavo-cel)	Mesothelin positive solid tumours	Autologous T-cell receptor therapy	Achieved combined 22% response rate in mesothelin positive patients with ovarian cancer and mesothelioma	Phase I/II
Alaunos Therapeutics	Library T-cell therapy	Advanced solid tumours	Autologous T-cell receptor therapy	Uses a non-viral 'Sleeping Beauty' gene delivery platform claimed to be more cost-effective with longer-term, stable gene expression	Phase I/II
Century Therapeutics	Stem cell-derived T and NK cell therapies	Haematological cancers and solid tumours	Allogenic T-cell therapy	Uses induced pluripotent stem cells (iPSC) to generate allogenic NK and T cells that may result in more streamlined and consistent products during manufacturing	Preclinical

Source: Edison Investment Research

Notable results that have appeared recently include Allogene Therapeutics' cell therapy ALLO-316, which has displayed encouraging anti-tumour activity in a Phase I study. While still very early days, management claims that 33% objective response rates represent one of the first clinical signs of an allogenic cell therapy achieving a positive impact on solid tumours. In what marked another achievement for the company, Allogene initiated what is believe to be the industry's first, potentially registrational Phase II allogenic CAR-T study in October 2022, which will investigate ALLO-501A in a subset of large B-cell lymphoma. Positive results in this trial would mark one of the most significant breakthroughs to date for 'off-the-shelf' therapies.

Despite clinical advancements, genetic engineering continues to be a time-consuming, complex and costly process – problems that Marker Therapeutics is attempting to address with its T-cell production platform, GRex. Marker's technology (MultiTAA) expands patients' (donor or own) naturally occurring tumour-specific T cells to be able to recognise up to five tumour-associated antigens, increasing the chances of eliciting a response in patients compared to single antigen-specific approaches. Marker's lead allogenic MultiAA product, MT-401, is in a Phase II study in AML, which may give indications of the clinical utility of non-genetically modified donor derived T-cell therapies.

With personalised therapies laying the groundwork, we believe it will only be a matter of time before key breakthroughs are observed in donor-derived treatments that, in our view, represent the future of the cell therapy field.

Gene therapies: A potentially longer road for new additions

Despite high-profile adverse patient events calling into question the safety of viral vectors, the clinical pipeline is packed with viral vector-based gene therapies so the technology is likely to be in use for the foreseeable future, certainly at least for the next wave of gene therapy approvals. Additionally, many gene therapy investigations continue to focus on rarer, as opposed to larger, disease indications. Smaller patient populations may be a contributing factor in keeping gene therapy prices at their current astronomical highs. However, the early-stage clinical pipeline is home to what may be considered advancements in the field (Exhibit 7).

Exhibit 7: Selected novel gene therapy approaches in biotech pipelines

Company	Drug	Indication/s	Gene technology	How it works	Clinical status
Regenxbio	RGX-314	Wet age-related macular degeneration (AMD)	NAV vector technology platform	Uses more advanced versions of viral vectors that have been developed to elicit enhanced gene expression and improved safety profile	Phase III Phase III
4D Molecular Therapeutics (4DMT)	4D-710 4D-310 4D-150	Cystic fibrosis Fabry disease Wet AMD	Targeted, disease-specific viral vector capsids	Disease-specific vector approach to develop customised vectors that can deliver gene therapies in a targeted manner to cells of interest in the body. Has potential to overcome limitations associated with existing viral vector technologies including toxicity	Phase I/II Phase I/II Phase I/II
Excision BioTherapeutics*	EBT-101	HIV	Viral vector-based CRISPR/Cas9	Removes large portions of HIV viral DNA through DNA cutting, which aims to deactivate the virus	Phase I
Lexeo Therapeutics*	LX1001	Alzheimer's disease	Disease tailored viral vectors	Delivers the human apolipoprotein E2 (APOE2) gene to express protective APOE2, which is thought to halt or slow progression in Alzheimer's	Phase I/II

Source: Edison Investment Research. Note: *Private companies

While we acknowledge the smaller patient cohort (n=5), gene therapy focused biotech 4DMT recently reported encouraging interim data from its Phase I/II study in wet AMD. Treatment with the disease-specific gene therapy product 4D-150 resulted in 80% of patients not requiring re-dosing for up to 10 months after administration combined with a reduction in annualised anti-VEGF injection rate by 96.7%. The company is also progressing studies in cardiological and pulmonological indications. The cystic fibrosis (CF) study is of particular interest as it represents a potentially sizeable market opportunity (estimated drug sales in 2028 of US$12.3bn for the CF market as a whole, according to Evaluate Pharma). Future CF drug sales are expected to be dominated by Vertex's twice-daily dosing Trikafta (estimated sales in 2028 of US$10.5bn, according to Evaluate Pharma) so approval of a genetic therapy may significantly disrupt this broader disease market.

Today's gene therapies focus on the delivery of new whole genes; however, gene-editing technologies (CRISPR/Cas9) aim to change an individual's underlying DNA to fix a defective gene. Viral vectors may be considered less durable than gene editing because when cells multiply the therapeutic gene is not replicated, becoming diluted and losing efficacy over time, so many see gene editing forging a new path in genetic medicine. There are some big players in the CRISPR camp, such as CRISPR Therapeutics and Intellia Therapeutics. However, Excision BioTherapeutics is applying the technology in an area where few have yet explored: infectious diseases. The private biotech initiated a first-in-human study in September 2022 applying CRISPR to treat HIV, and we will be watching future safety and clinical proof of concept demonstrations from EBT-101 closely.

Lexeo Therapeutics is also looking to break the mould in targeting not only larger diseases but those acquired during a person's lifetime rather than inherited at birth, and it does not come much bigger than going after Alzheimer's disease (AD). In what is arguably one of the most talked about and unmet disease areas (see our recent report for our prospectus on the current neuroscience landscape), Lexeo is targeting a subset of AD patients who possess the APOE4 gene. APOE4 is thought to exist in up to 25% of the AD population and homozygous carriers (those with two

identical copies of the gene) are believed to be c 15 times more likely to develop the disease. The study marks one of the only active industry-sponsored AD trials investigating gene therapy treatment and Lexeo is being backed in its endeavours to continue development in both large and rare diseases.

It is likely to take many years before we see any major breakthroughs for gene therapy into indications that affect the broader population; however, albeit currently sparse, there will almost certainly be an increasing trend of emerging biotechs planting their flags in the grounds of the larger disease markets.

Reimbursement: Where science meets reality

If getting drug approval is not tough enough, one of the biggest sticking points that CGTs, particularly gene therapies, face will be securing reimbursement. With such high prices, biopharmas face the difficult task of convincing payers of not only the beneficial value their drugs bring to patients but also the savings they could potentially provide healthcare systems (Exhibit 8).

Exhibit 8: FDA approved cell and gene therapy pricing

Company	Drug	List price (cost per patient) US$	Drug type
BioMarin	Roctavian*	1.9–2.5m (est) per treatment	Gene therapy
CSL Behring	Hemgenix	3.5m per treatment	Gene therapy
Bluebird bio	Skysona	3m per treatment	Gene therapy
Bluebird bio	Zynteglo	2.8m per treatment	Gene therapy
Johnson & Johnson	Carvykti	465k per course	Gene-modified cell therapy
Bristol Myers / Bluebird bio	Abecma	420k per course	Gene-modified cell therapy
Bristol Myers	Breyanzi	410k per course	Gene-modified cell therapy
Gilead / Kite	Tecartus	373k per course	Gene-modified cell therapy
Novartis	Zolgensma	2.1m per treatment	Gene therapy
Roche / Spark	Luxturna	850k (425k per eye)	Gene therapy
Gilead / Kite	Yescarta	373k per course	Gene-modified cell therapy
Novartis	Kymriah	475k per course	Gene-modified cell therapy
	Median gene therapy	2.5m	
	Median gene-modified cell therapy	415k	

Source: Edison Investment Research, Evaluate Pharma, FDA cell and gene therapy approvals. Note: *EU list price €1.5m.

With only a limited number of CGTs approved that target smaller disease populations, payers have shown willingness to adopt new payment strategies that include installment-based payments and patient outcomes-based reimbursement. However, as more CGTs come to market and potentially move into more prevalent diseases it is unclear how scalable or sustainable such approaches will continue to be, with many anticipating health systems to experience potential 'cost shocks'. Even today, creative reimbursement models may not be enough to gain buy-in from payers, something Bluebird bio experienced firsthand. Having initially brokered a deal with German payers through a patient outcome fixed installment plan for Zynteglo, subsequent negotiations broke down resulting in Bluebird having to withdraw its drug from the German market, closely followed by a strategic decision to exit Europe altogether. Moreover, payers often experience high churn rates of their beneficiaries, making it difficult to maintain longer-term contracts for one-time treatments once patients have received them.

While the current reimbursement situation paints a relatively murky picture, the situation is not devoid of solutions and there is a consensus across healthcare ecosystems of the need to adapt. However, this will require closer and earlier engagement between biopharmas and payers to devise novel financing mechanisms that provide greater access to potentially life-changing therapies for patients. Novartis is leading by example and has worked closely with both US and European agencies to promote the therapeutic value of Zolgensma. It has since been able to negotiate 80% coverage from Medicaid and commercial payers in the United States, while the 'Day One' scheme rolled out in Europe provides patients with upfront access to treatment, followed by staged

payments, with Novartis guaranteeing rebates once payers have valued the economics of the drug following national or local health technology assessments.

Such innovative methods combined with closer, positive relationships between governments, commercial payers and industries, we believe, will be critical if CGTs are to not only become commercial successes but truly bring about major change to the therapeutic landscape and live up to their hype.

CGTs a potentially hot space but have a way to go

CGTs will continue to be a market that draws heightened interest and investment from big pharma. While significant financial returns and straightforward commercialisation paths appear to be in the distant future, if CGTs do deliver on what they have promised, we believe the most successful investment in this space will be those biotechs housing the best-in-class researchers, patent portfolios and technologies. In our view, this is where the true value of CGT biotechs lies and gaining access to this value may be what, in the end, can generate the greatest returns on investment for shareholders.

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Frankfurt +49 (0)69 78 8076 960
Schumannstrasse 34b
60325 Frankfurt
Germany

London +44 (0)20 3077 5700
280 High Holborn
London, WC1V 7EE
United Kingdom

New York +1 646 653 7026
1185 Avenue of the Americas
3rd Floor, New York, NY 10036
United States of America

Sydney +61 (0)2 8249 8342
Level 4, Office 1205
95 Pitt Street, Sydney
NSW 2000, Australia