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From pipeline to pricing and reimbursement: trends in the gene therapy landscape and implications for the future

Evie Cooke, Mark Orchard

EXECUTIVE SUMMARY

Background

The field of gene therapy finds itself at a critical juncture. While 2024 marked a record year for FDA approvals of cell and gene therapies (CGTs), and the clinical pipeline continues to expand, the sector faces significant challenges (1, 2). The initial enthusiasm has given way to a more complex reality, as commercial hurdles have led some investors to reassess their commitments (notably more recently Pfizer with Beqvez and Bluebird bio's cheap sale). The rate of regulatory approvals is expected to continue increasing, with some estimates projecting that by 2030 as many as 74 CGTs could be approved in the US along with 44 approved in Europe (3, 4). This evolving landscape presents both opportunities and obstacles, making it a pivotal and transformative period for the industry.

Sarepta Therapeutic's Elevidys (delandistrogene moxeparvovec-rokl), became the world's first gene therapy approved for Duchenne muscular dystrophy (DMD) in 2023 priced at $3.2 million, and generated $200 million in sales in its first year on the market (5, 6). Elevidys exemplifies a shift in the gene therapy pipeline away from ultra-orphan target indications, which have traditionally dominated, to more prevalent (but still rare diseases) such as DMD; one of the most frequent genetic conditions affecting approximately 1 in 3,500 male births worldwide (7). In February 2024, the FDA accepted an efficacy supplement to expand Elevidys' indication by removing age and ambulation restrictions; thereby further widening the target patient population (8). Elevidys is a classic example of a "one-and-done" treatment that refers to a gene therapy expected to require a single administration for lifetime efficacy. Such high-cost gene therapies present challenges for payers who are increasingly concerned with ensuring sustainable budget impact while maintaining patient access amid increasing gene therapy approvals in the coming years. Indeed, in 2023 Lenmeldy became the world's most expensive therapy priced at $4.25 million in the US (9). Many question whether the precedent for the high prices seen for approved gene therapies to date can continue or whether the trend towards increasing prices and larger indications will give rise to a perfect storm of access and reimbursement struggles. In this case, alternative reimbursement models to manage uncertainties regarding affordability and duration of treatment effect could prove paramount.

Methods/scope

In 2021, Cogentia published a comprehensive analysis of the gene therapy pipeline, comparing the commercial attractiveness of pipeline indications and predicted challenges sustaining the financing of an increasing gene therapy pipeline targeting rare diseases with high price tags. This whitepaper reflects on those themes and provides an updated review of the gene therapy pipeline to date. This includes an analysis of emerging trends in the current gene therapy pipeline and the implications for both payers and manufacturers in the future.

Gene therapy is defined here as *in vivo* gene replacement therapies unless stated otherwise, with chimeric antigen receptor T cells (CAR-Ts) and cell therapies largely out of scope of this report. We analysed a pipeline sample of 113 gene therapies in clinical stage development at the time of writing in January 2025. Cogentia presents a budget impact analysis of five recently launched or near-term gene therapies (defined as a gene therapy expecting regulatory approval and launch between 2025 and 2027) as well as an assessment of the potential commercial attractiveness, relating to the following factors: prevalence, age of eligibility, disease burden, healthcare resource use, current treatment options and cost of comparator. We also investigate how pricing and reimbursement models for gene therapies have varied by geography and how they may evolve in the future into one mechanism for stakeholders to manage uncertainty.

Results

Our analysis reveals a dynamic landscape in gene therapy development and commercialisation. Metabolic disorders dominate the pipeline, comprising ~21% of clinical stage therapies, with a notable shift towards more prevalent diseases (29.2% of assets, up 14.2% since previous analysis in 2021). Furthermore, commercial attractiveness varies significantly across indications, with scores ranging from 0.3 to 3.3 out of 4 on our proprietary matrix, highlighting the need for tailored market access strategies. As anticipated, budget impact assessments for prevalent conditions such as severe haemophilia A and DMD project potential billion-dollar annual costs, raising concerns about healthcare system sustainability, although based on precedent actual uptake is likely to be substantially lower than forecasted. Analysis also highlights how real-world challenges have emerged, exemplified by Roctavian's struggles in haemophilia A and Pfizer's discontinuation of Beqvez in haemophilia B, underscoring issues with patient hesitancy and reimbursement. These findings emphasise the critical importance of robust value demonstration, strong pricing models, and early stakeholder engagement to navigate the evolving gene therapy landscape successfully.

Conclusions

In conclusion, the gene therapy landscape is evolving rapidly, with a notable shift towards targeting more prevalent diseases. This transition brings both opportunities and challenges, as exemplified by the struggles of therapies like Roctavian in haemophilia A. While the potential for transformative treatments remains high, the industry is adopting a more cautious approach in light of real-world implementation challenges. As gene therapies continue to advance, stakeholders must balance the promise of innovative treatments with practical considerations of cost, patient acceptance, and healthcare system integration. The coming years will be critical in determining how gene therapies can fulfil their potential to revolutionise treatment paradigms across a broader range of diseases and whether the clinical profiles can translate into commercial success.

Evie Cooke
Analyst, Cogentia
evie.cooke@cogentia.co.uk

Mark Orchard
Senior Consultant, Cogentia
mark.orchard@cogentia.co.uk

INTRODUCTION

The conception of gene therapies can be traced back to the 1960s, which saw the first laboratory evidence for the uptake and expression of exogenous DNA in mammalian cells (10). In the early 1970s, Theodore Friedmann and Richard Roblin were the first to propose the application of recombinant DNA techniques to human disease, suggesting tumour viruses could deliver genetic material to correct disease phenotypes in humans (10). Since then, thousands of cell and gene therapy (CGT) clinical trials have been conducted around the world, and in 2004 China became the first country in the world to approve a gene therapy-based product for clinical use with Gendicine; an *in vivo* adenoviral-based therapy for head and neck carcinoma (11).

Figure 1: ***In Vivo*** **and** ***Ex Vivo*** **gene therapies**

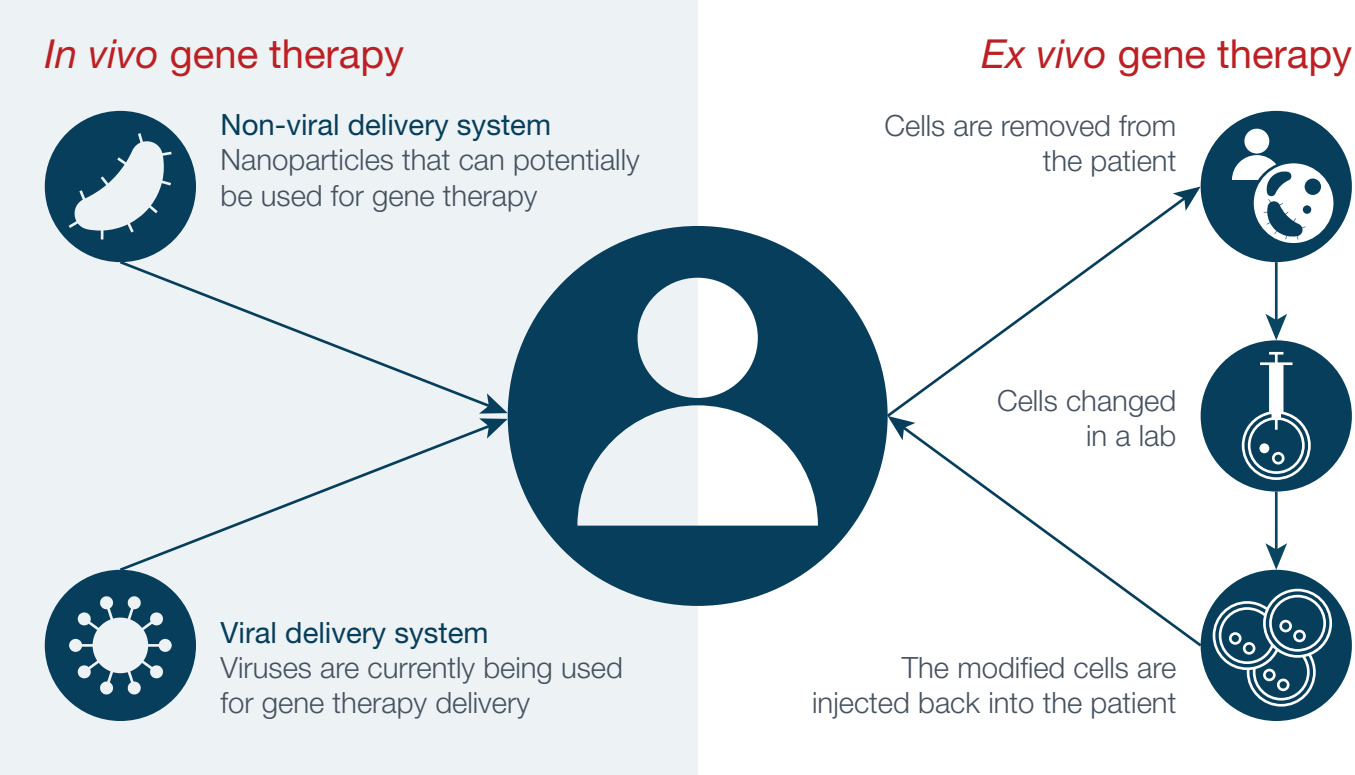


Figure adapted from Heuvel et al (2020) (12)

DEFINING "GENE THERAPY"

Broadly, gene therapies can be classified into three distinct categories: gene silencing, gene replacement and gene editing, with each method capable of being achieved *in vivo* or *ex vivo* (Figure 1).

To date, the gene therapy landscape largely consists of *in vivo* gene replacement methods using viral vectors as well as *ex vivo* CD34+ gene therapies such as Zynteglo.

For the purposes of this whitepaper, gene therapy herein refers to *in vivo* gene replacement therapies unless stated otherwise, with chimeric antigen receptor T cells (CAR-Ts) and cell therapies out of scope for the analysis of this report.

The gene therapy pipeline has been slowly expanding in recent years, with an increasing number of assets in preclinical development over time, but the more expensive late-stage development has plateaued and even shows signs of declining (13). Since 2013, the number of gene therapies launched globally has more than doubled (14). As of January 2025, there are now 43 CGTs approved in the US and 19 gene therapies (including genetically modified cell therapies) still approved in Europe (15, 16).

The number of approved gene therapies is set to continue increasing in the future, with some estimates projecting that by 2030 as many as 74 CGTs could be approved in the US along with 44 approved in Europe (3, 4).

The recent increase in gene therapies reaching the market is underpinned in part by technological advances; for example, in bioengineering viral vectors to improve efficacy and safety as well as breakthroughs in genomics, with next-generation sequencing revealing novel disease targets (17). Novel gene editing technologies such as clustered regularly interspaced short palindromic repeats (CRISPR) are also gaining attention and supporting pipeline growth, with Vertex Pharmaceuticals securing the world's first approval of a CRISPR therapy following the Medicines and Healthcare products Regulatory Agency (MHRA) approval of Casgevy in the UK in November 2023, US Food and Drug Administration (FDA) approval in 2023 and European Medicines Agency (EMA) approval in 2024 (15, 16, 18). CRISPR technology can potentially target a broader range of diseases compared with traditional adeno-associated virus (AAVs)-based gene therapies. Unlike AAVs, which are limited by the size of the genetic material they can deliver and specific targeting capabilities, CRISPR offers more precise and flexible gene editing capabilities. This allows for the correction of a wider variety of genetic mutations and the possibility of treating diseases that were previously difficult to target; thereby expanding the horizons of the gene therapy pipeline.

These technological advancements and the associated pipeline expansion have encouraged investment in the modality, as presented in Table 1 (13).

Vertex CEO told investors that the company had hit the ground running, claiming that

> *"physicians prefer gene editing therapy to gene therapy"*

During the COVID-19 pandemic, investment in CGTs saw a significant increase, with funding peaking at $19.9 billion in 2020 and $22.7 billion in 2021 (19). This was fuelled by heightened interest in innovative therapies and the broader biotech sector during the global health crisis. A survey conducted during the pandemic revealed that 78% of CGT professionals believed COVID-19 positively impacted investment in the sector, reflecting a strong sentiment for growth and innovation during this time (20).

After the initial boom, investments have dropped significantly, reaching $12.6 billion in 2022 and $11.7 billion in 2023. This decline has led to budget cuts, layoffs, and reduced activity among CGT companies. The current sentiment reflects a more cautious approach from investors, driven by rising interest rates, limited initial public offering (IPO) activity, and challenges in translating early-stage innovations into commercial success. Roche acquired Spark Therapeutics in 2019 for $4.8 billion, paying a substantial premium to secure assets like Luxturna (the first FDA-approved gene therapy for an inherited disease) and a promising haemophilia asset (21). Despite initial optimism, Roche has since written off much of Spark's value due to slower-than-expected returns on investment and broader challenges in the CGT market. This highlights how inflated valuations during the pandemic are now being reassessed under current market conditions (19).

Table 1: Examples of Recent CGT Deals (2023-2024)

Company A	Company B	Deal type	Deal value	Date announced
Kyowa Kirin	Orchard Therapeutics	Acquisition	$477m	January 2024
Tome Biosciences	Replace Therapeutics	Acquisition	$185m	January 2024
AstraZeneca	Cellectis	Equity investment	$140m	May 2024
Novartis	Kate Therapeutics	Acquisition	$1.1bn	November 2024
Roche	Poseida Therapeutics	Acquisition	$1.5bn	November 2024

Sources: company press releases (22-26)

THE ISSUE OF SUSTAINABILITY IN THE GENE THERAPY PIPELINE

Long considered the holy grail of precision medicine, gene therapies target the underlying genetic and molecular drivers of disease and offer the potential to claim curative intent, a once unimaginable goal. The development of such novel advanced therapies is not cheap, with one study reporting a single gene therapy's clinical stage R&D alone can cost an average $1.94 billion (27). Thus, from a manufacturer's perspective, for the continuing development of gene therapies to be sustainable, significant commercial sales and return on investment (ROI) are expected. To date, given the low volume ultra-orphan indications targeted thus far, the predominant way to achieve ROI has been through unprecedented price tags. Lenmeldy, the one-time gene therapy for metachromatic leukodystrophy made headlines as it became the world's most expensive drug with a price of $4.25 million per treatment in the US (9). Such gene therapies are unlikely to meet payer affordability thresholds and present unique reimbursement challenges for national healthcare systems that remain largely constrained under traditional healthcare models that rely on regular, predictable, repeat payments attributable to chronic disease treatments. Given their one-and-done nature, gene therapies do not follow the typical commercial trajectory of chronic treatments. Rather than treating a base of prevalent patients, supplemented by the incident population, gene therapies (e.g. Zolgensma) have often treated the prevalent population within 3-5 years, after which time only incident patients are treated.

DEFINING PREVALENT, RARE AND ULTRA-RARE DISEASES

Prevalent diseases:
Defined in Europe as a disease affecting more than 5 in 10,000 people.

Rare disease:
Defined in Europe as a disease affecting no more than 5 in 10,000 people.

Ultra-rare disease:
Defined here as a disease affecting fewer than 1 in 50,000 people.

Gene therapies demanding high upfront price tags and claiming durable long-term effects (often with limited duration of follow up to substantiate this claim), are thus forcing a shift in this paradigm as payers must balance access with affordability and uncertainty arising from the typically insufficient data supporting claims at the time of launch (28). With the trend of increasing gene therapy approvals and a seemingly growing shift to targeting more prevalent indications, national payers are under mounting pressure to ensure patient access while minimising budget impact and uncertainty wherever possible, as a matter of sustainability. There is a need to better understand the likely opportunities and challenges the current gene therapy pipeline will present for future payers and manufacturers.

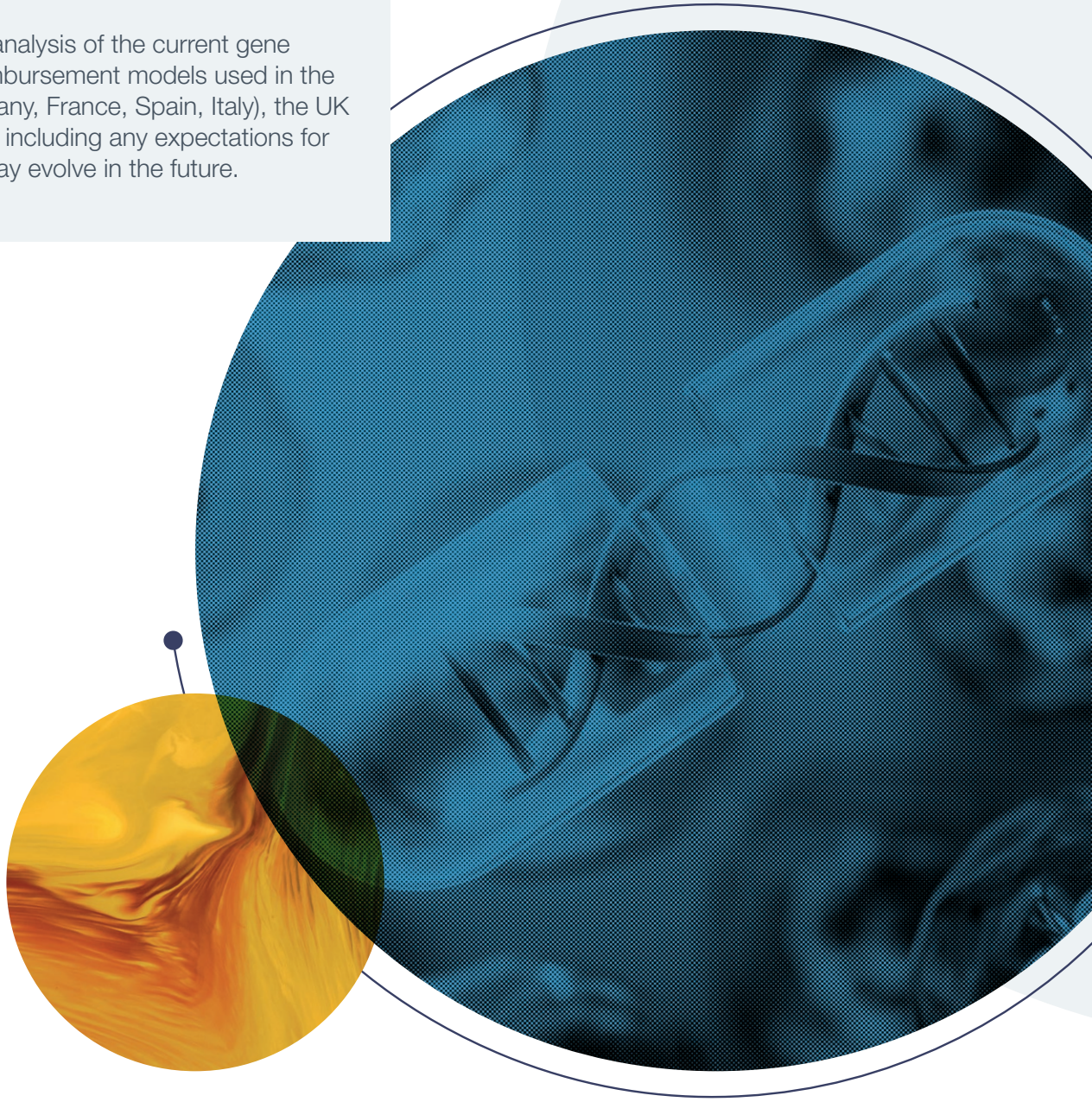
As such, the aims of this whitepaper are to:

1. Identify emerging trends in the gene therapy pipeline and comment on their implications for both payers and manufacturers.

2. Provide a budget impact analysis of five gene therapies that are due to launch in the next 5 years and comment on access challenges and opportunities.

3. Investigate the commercial viability of ten near to launch gene therapies.

4. Provide an analysis of the current gene therapy reimbursement models used in the EU4, (Germany, France, Spain, Italy), the UK and the US, including any expectations for how they may evolve in the future.



CHAPTER 1: ANALYSIS OF THE GENE THERAPY LANDSCAPE TO DATE IN Q4 2024

To anticipate future market access implications of the gene therapy pipeline, it is useful to first examine historical trends within gene therapy access that may set precedent for emerging challenges. While there were a total of 23 gene therapies (including genetically modified cell therapies) approved in the US or Europe in June 2024 (Table 2), it began with the approval of UniQure's Glybera in Europe.

Today, Glybera is absent from the list of current approved gene therapies (Table 2), having proved a major commercial flop, withdrawing its EMA marketing authorisation in 2017. The EMA made the landmark approval of Glybera in 2012 for the treatment of familial lipoprotein lipase deficiency (LPLD); an ultra-rare condition affecting approximately one in a million people. Despite an encouraging clinical profile and promising therapeutic effects, Glybera experienced extremely limited patient uptake (with only one patient ever reported to receive the drug commercially) as well as a prohibitively high price tag at the time of €1 million per dose resulting in low demand.

Table 2: FDA and EMA Approved Gene Therapy Products (Including Genetically Modified Cell Therapies) as of Q4 2024

Product name	Generic name	Originator company	Modality	Disease (s)	Year first approved	Locations approved
Aucatzyl	Obecabtagene autoleucel	Autolous Therapeutics	CAR-T	Leukaemia	2024	US
Tecelra	Afamitresgene autoleucel	Adaptimmune Therapeutics plc	Genetically modified autologous T- cell immunotherapy	Unresectable or metastatic synovial sarcoma	2024	US
Beqvez	Fidanacogene elaparvovec-dzkt	Pfizer	AAVRh74var gene therapy	Haemophilia B	2024	EU, Canada, US
Casgevy	Exagamglogene autotemcel	Vertex	CRISPR modified stem cells	Sickle cell disease; beta thalassaemia	2023	US, EU, UK
Elevidys	Delandistrogene moxeparvovec-rokl	Sarepta Therapteutics	AAVRh74	Duchenne Muscular Dystrophy	2023	US
Lyfgenia	Lovotibeglogene autotemcel	Bluebird	Genetically modified autologous CD34+ HSCs	Sickle cell disease	2023	US
Vyjuvek	Beremagene geperpavec	Krystal Biotech	HSV-1 gene therapy	Epidermolysis bullosa	2023	US
Adstiladrin	Nadofaragene firadenovec	Merck	Adenoviral gene therapy	Bladder cancer	2022	US
Hemgenix	Etranacogene dezaparvovec	UniQure	AAV5 gene therapy	Haemophilia B	2022	US, EU, UK
Roctavian	Valoctocogene roxaparvovec	BioMarin	AAV5 gene therapy	Haemophilia A	2022	EU, UK
Upstaza	Eladocagene exuparvovec	PTC Therapeutics	AAV2 gene therapy	Aromatic L-amino acid decarboxylase (AADC) deficiency	2022	US, EU, UK
Carvykti	Cilta-cel	Legend Biotech	CAR-T	Myeloma	2022	US, EU, UK, Japan
Skysona	Elivaldogene autotemcel	Bluebird Bio	Genetically modified autologous CD34+ HSCs	Adrenoleukodystrophy	2021	US (was approved in the EU then withdrawn)
Abecma	Idecabtagene vicleucel	Bluebird Bio	CAR-T	Myeloma	2021	US, EU, UK, Canada, Japan
Breyanzi	Lisocabtagene maraleucel	Bristol Myers Squibb	CAR-T	Diffuse large B-cell lymphoma and follicular lymphoma	2021	EU, UK, US, Japan, Canada, Switzerland
Libmeldy	Atidarsagene autotemcel	GSK	Genetically modified autologous CD34+ HSPCs	Leukodystrophy, metachromatic	2020	EU, UK, US
Tecartus	Brexucabtagene autoleucel	Gilead Sciences	CAR-T	Acute lymphocytic leukaemia and mantle cell lymphoma	2020	EU, UK, US, Australia
Zynteglo	Betibeglogene autotemcel	Bluebird Bio	Genetically modified autologous CD34+ HSCs	Thalassemia	2019	US (was approved in the EU then withdrawn)
Zolgensma	Onasemnogene abeparvovec	AveXis/Novartis	AAV9 gene therapy	Muscular atrophy, spinal	2018	Australia, EU, Japan, US, Brazil, Canada, Israel, China, UK
Luxturna	Voretigene neparvovec	Roche	AAV2 gene therapy	Leber's congenital amaurosis; retinitis pigmentosa	2017	Canada, US, Australia, EU, UK, South Korea
Yescarta	Axicabtagene ciloleucel	Gilead Sciences	CAR-T	Cancer, lymphoma, B-cell, diffuse large, Cancer, lymphoma, follicular	2017	Japan, China, Canada, EU, US, UK, Australia
Kymriah	Tisagenlecleucel	Novartis	CAR-T	Acute lymphocytic leukaemia and diffuse large B-cell lymphoma and follicular lymphoma	2017	US, EU, UK, Japan, Australia, Switzerland, Canada, South Korea
Strimvelis	Autologous CD34+ enriched cells	GSK	Genetically modified autologous CD34+ HSPCs	Adenosine deaminase deficiency	2016	EU, UK
Imlygic	Talimogene laherparepvec	Amgen	Oncolytic virus	Melanoma	2015	EU, UK, US, Australia
Neovasculgen	Vascular endothelial growth factor (VEGF)	Human Stem Cells Institute	Plasmid vector gene therapy	Ischaemia, limb; peripheral vascular disease	2011	Russia, EU

Source: (29)

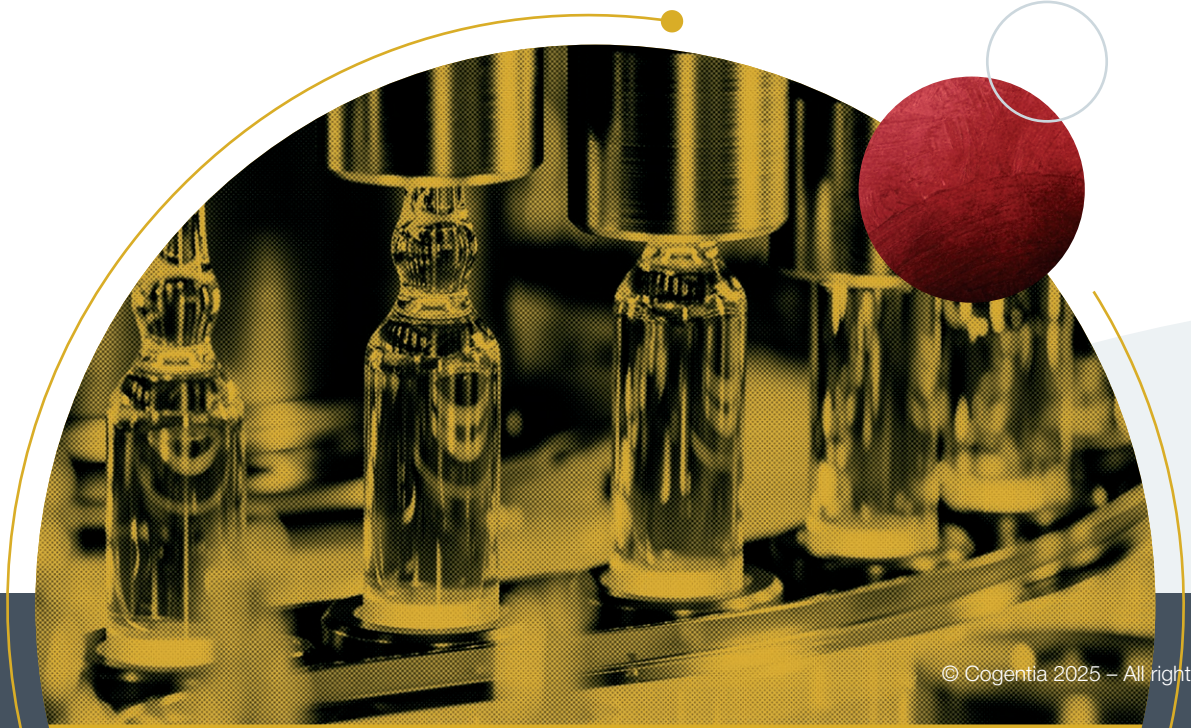
In vivo gene replacement therapies; the focus of this whitepaper

Glybera's story would prove reflective of a wider trend for gene therapy manufacturers to target rare diseases in subsequent approvals and a cautionary tale of the access and uptake challenges that accompany this strategy (Table 3). Exemplifying this, 4 years after Glybera's approval, Orchard Therapeutic's (but originally GSK's) Strimvelis for ultra-rare severe combined immunodeficiency due to adenosine deaminase deficiency was approved by the EMA in 2016 and experienced similar uptake struggles, eventually resulting in Orchard Therapeutic's discontinuation of the asset in 2022 (30).

Table 3: Access Challenges Associated With the Commercialisation of Gene Therapies for Rare Diseases as Viewed by Different Stakeholders

Gene therapy access challenge	Manufacturer	Payer	Patient
Small clinical trials*	Challenging patient identification and clinical trial recruitment. Small eligible patient population.	Small clinical trials mean there is a high level of uncertainty in the data available at assessment.	
Demonstrating duration of effect	A robust evidence package is required to claim sustainable duration of therapeutic effect, i.e. long-term benefits.	Payers may face great uncertainty from short-term clinical trial data as to the duration of benefit.	Patients may be expected to continually monitor for and report adverse events which can be burdensome.
Cheaper standard of care comparator	Manufacturers may face pricing challenges in justifying a high upfront cost against comparatively cheap standard of care comparators.	Payers such as that in the UK concerned about cost-effectiveness may struggle to accept higher prices against a low-cost high standard of care.	
High price	Manufacturers need to recoup R&D investment and a small patient pool increases the need for higher price points.*	Payers are faced with budget impact and cost-effectiveness concerns when gene therapy prices are high.	Patients may feel guilt accessing high-cost treatment that is funded by national healthcare providers or experience worry around patient co-pay schemes required to access the medicine.
Logistical challenges	Manufacturers may face challenges establishing a reliable supply chain for administration of the therapy.	Dedicated and specialist trained healthcare professionals are often required to administer gene therapies – representing a significant healthcare resource utilisation and cost.	Accessing the few specialist treatment centres or clinical trials may be challenging for patients who are geographically disadvantaged.

**Unique to gene therapies targeting rare diseases.*

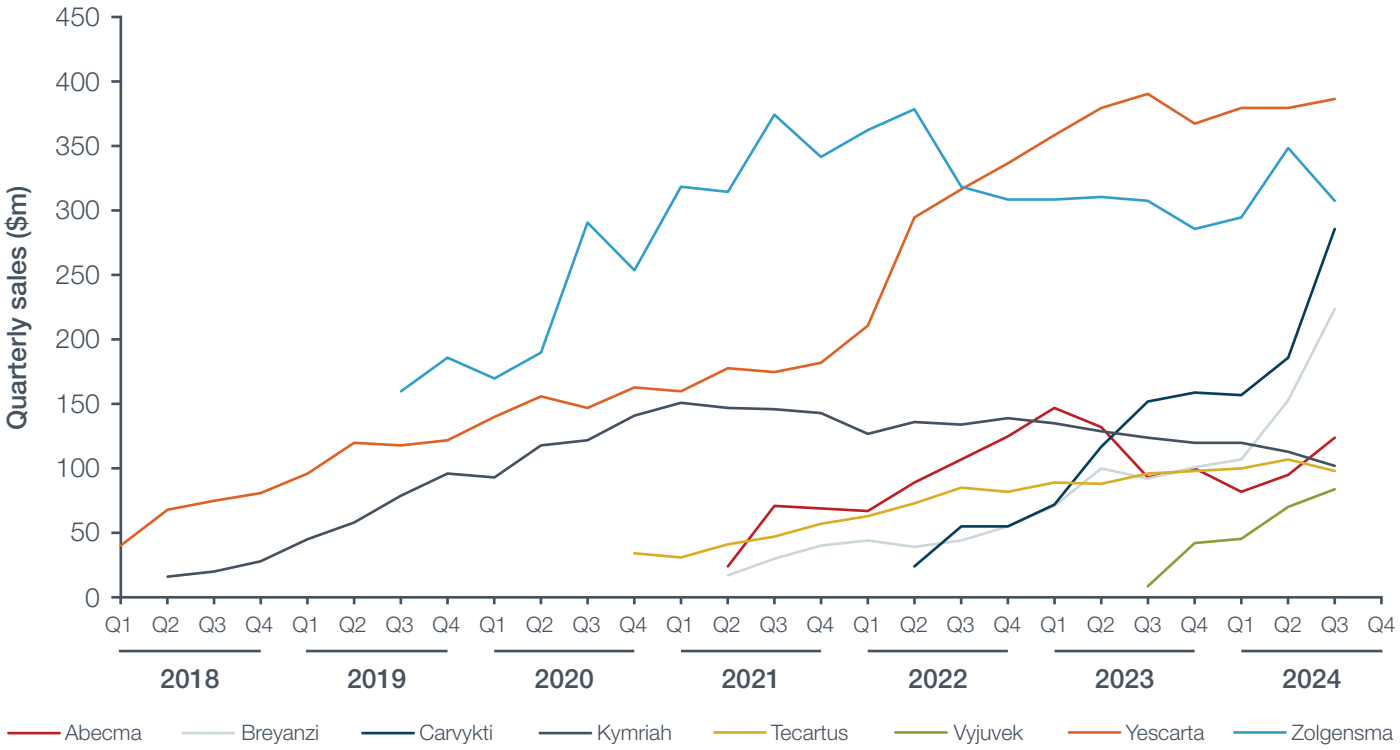


ZOLGENSMA: A CASE STUDY IN GENE THERAPY'S COMMERCIAL PROMISE

The access and uptake challenges that have plagued gene therapies targeting rare diseases raise questions as to why manufacturers commit to this strategy. The strategic focus towards orphan diseases seen to date has been driven by a combination of regulatory incentives, such as tax credits, research grants, and extended market exclusivity, as well as commercial factors, including high unmet need and small patient populations, which typically drive premium price potentials while limiting clinical trial costs.

Novartis' Zolgensma is one example of a gene therapy that has succeeded in capitalising on these incentives and secured notable commercial success relative to other gene therapies (Figures 2 and 3).

Figure 2: CGT Quarterly Sales (Q1 2018-Q3 2024)



Note: *The CGTs selected have cumulative revenue >$50m Q1 2018 to Q3 2024. Q4 2024 revenue data were not available at the time of writing.*

Source: data from company financial reports

AveXis' (a Novartis subsidiary) Zolgensma was first approved by the FDA in 2019 for paediatric patients less than 2 years of age with 5q spinal muscular atrophy (SMA) (31). SMA is a rare genetic disease, affecting approximately 0.4 in 10,000 people; translating to a patient population of less than 21,000 in Europe (32). SMA type 1 is the most common form of the disease (accounting for 60% of cases), which manifests in early infancy due to a mutation or absence of the survival motor neuron gene 1 (SMN1). Children with this condition are unable to sit up and quickly experience severe swallowing and breathing difficulties, necessitating the use of feeding tubes and mechanical ventilation. Without intervention, the prognosis is usually fatal by 2 years old (33).

Priced at $2.1 million, Zolgensma was the world's most expensive drug in 2019 and caused significant publicity concerns at the time around the affordability of gene therapies (34). The Institute for Clinical and Economic Review (ICER) report for Zolgensma stated, "…at a placeholder price of $2 million, our base-case results found that it too does not meet traditional cost-effectiveness benchmarks for use for patients with type 1 SMA", and went on to suggest Zolgensma's price should be "reduced to under $900,000 for the one-time administration to meet a $150,000 per [quality adjusted life year] QALY threshold" (35). Furthermore, Zolgensma's single-arm trial included narrow eligibility criteria and small participant numbers, which limited the generalisability of data to the broader SMA population, particularly those more severely affected or with comorbidities. This meant reimbursement and coverage restrictions were required to ensure treatment effect and cost-effectiveness were maintained. For example, the National Institute for Health and Care Excellence (NICE) restricted patient age to 6 months or younger or 7-12 months if agreed by a multidisciplinary team, and a further restriction that the gene therapy only be used for type 1 SMA with a bi-allelic mutation in the SMN1 gene (33).

Additionally, payers were faced with a lack of long-term safety and efficacy data meaning the durability of Zolgensma's gene therapy remained uncertain. Indeed, in NICE's assessment of Zolgensma under the highly specialised technology route, this uncertainty was reflected in the need to reduce the QALY weighting used in decision-making (36).

However, despite these challenges and the headwinds of targeting a rare disease, Zolgensma's commercial success prevailed. Following US regulatory approval, Zolgensma showcased rapid uptake, treating 100 US patients per quarter by Q2 2020, which translated into $170 million in sales (37). EMA approval in 2020 and subsequent European and then international reimbursement approvals further contributed to growth (Figure 3). In Q3 2024, Zolgensma had launched in over 55 countries. After experiencing strong initial growth, Zolgensma sales have plateaued and are now showing signs of decline, as the drug's market has largely shifted from the existing patient pool to newly diagnosed cases (Figure 3). This transition from prevalent to incident population limits sales growth, making geographic expansion crucial for increasing revenue.

Novartis is now planning the launch of an intrathecal (spinal cord delivery) Zolgensma. In January 2025, Novartis released positive data from the randomised phase 3 trial (Steer) showing it met its primary endpoint, which is measured by the Hammersmith Functional Motor Scale-Expanded score, an industry scale that assesses the motor ability of patients with SMA (38).

Intrathecal delivery has advantages over intravenous delivery including smaller doses that are not dependent on a patient's weight, thereby limiting toxicity concerns. Due to Zolgensma's age or weight limitation in Europe, Novartis estimates more than 70% patients living with SMA have never had Zolgensma. It is hoped this new administration route will enable a larger and older patient population to be treated with Zolgensma in the future (39).

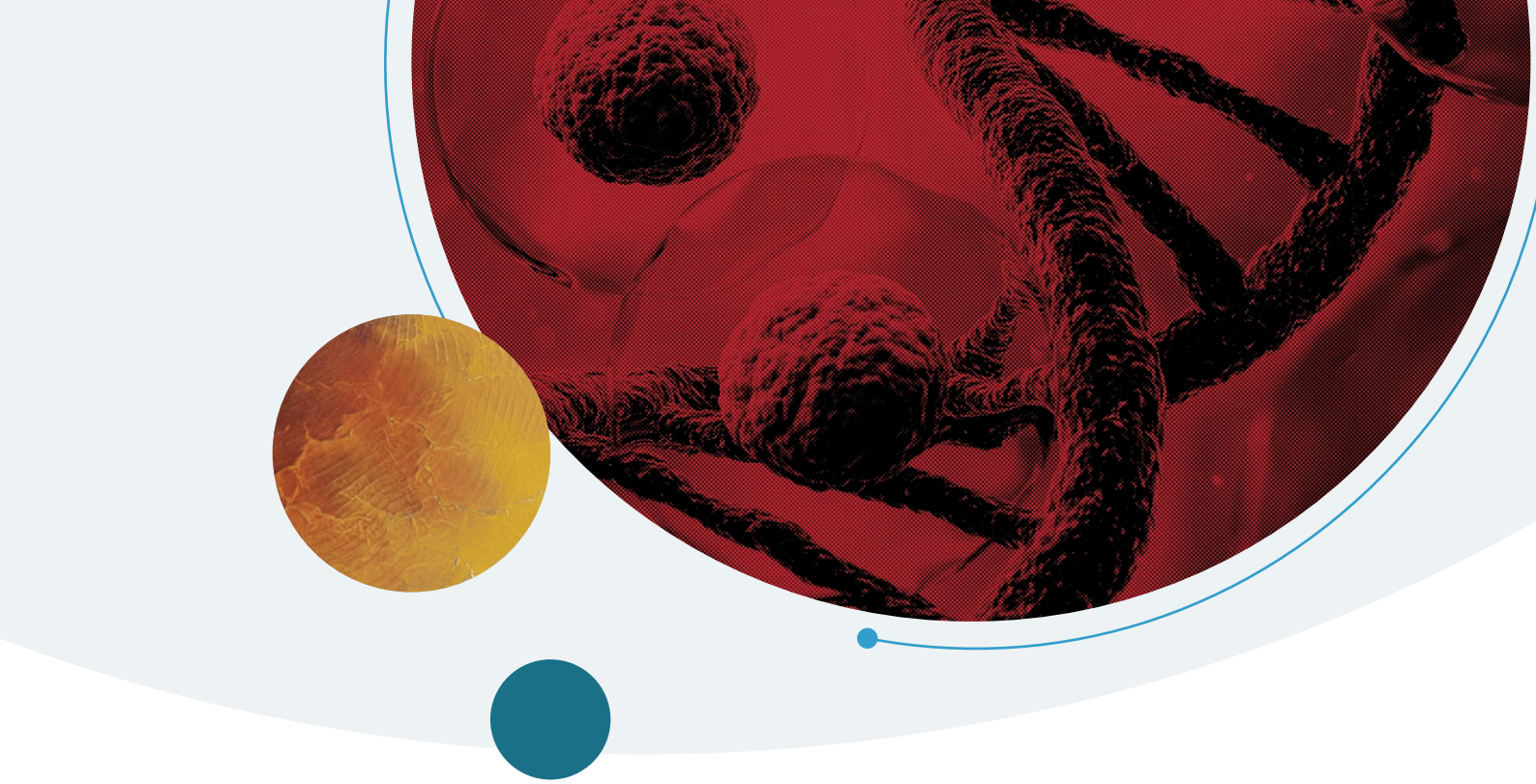
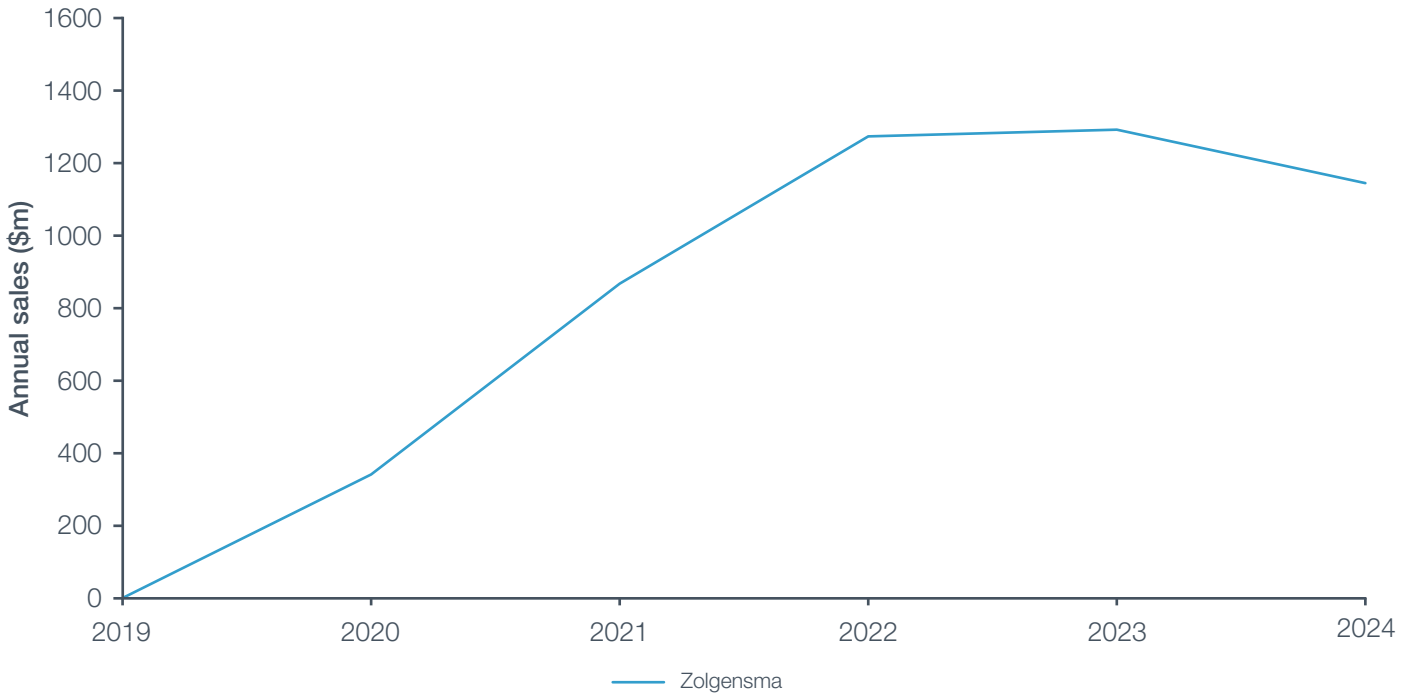


Figure 3: Zolgensma Commercial Performance



Source: Swissinfo.ch data (40)

Alongside achieving strong newborn genetic screening rates that enabled patients to be identified as soon as possible, perhaps the greatest contributing factor to Zolgensma's overall commercial success was its implementation of the "Day One" access programme (41). The "Day One" programme is a type of managed-entry agreement (MEA), incorporating elements such as annual staged payments, retroactive rebates, and outcomes-based rebates, as well as training for healthcare professionals and access to a global registry of patients living with SMA (37).

For Zolgensma, use of such MEAs enabled rapid access following EMA approval, before lengthy national pricing and reimbursement decisions had been concluded.

MANAGED-ENTRY AGREEMENTS – A SILVER BULLET FOR SUCCESSFUL PRICING AND REIMBURSEMENT?

MEAs have additional benefits beyond the potential to expedite access as showcased by Zolgensma.

On the surface, MEAs present notable benefits for drug reimbursement strategies (Table 4). Specifically, MEAs, such as outcomes-based rebate agreements, can mitigate financial and clinical uncertainty for payers by linking payments to agreed clinical outcomes. This approach can substantially reduce budget impact risks, particularly for high-cost gene therapies, by avoiding high upfront investments in the absence of robust efficacy data. Beyond cost containment and supporting sustainable healthcare financing, MEAs promote patient access and facilitate the collection of real-world evidence to inform reimbursement decisions (28).

However, MEAs can also present several challenges for drug reimbursement (Table 4). One major issue is the complexity and administration burden associated with implementing these agreements, particularly outcomes-based MEAs, which require extensive data collection and monitoring to assess treatment efficacy and safety over time. It is also a challenge to define relevant outcomes that are objective and easy to track during MEAs. The need for continuous evidence generation and the potential for delayed decision-making can pose significant hurdles for such agreements. Furthermore, there is evidence some countries such as Italy who have historically demonstrated a reliance on outcomes-based MEAs (Figure 4) have not received adequate value for money through MEAs. One observational study of the outcomes of MEAs in Italy between 2009 and 2021 found the median proportion of payback to expenditure was just 3.8%, concluding, “MEAs have limited importance for managing pharmaceutical expenditures… and improving implementation is a valuable consideration” (42).

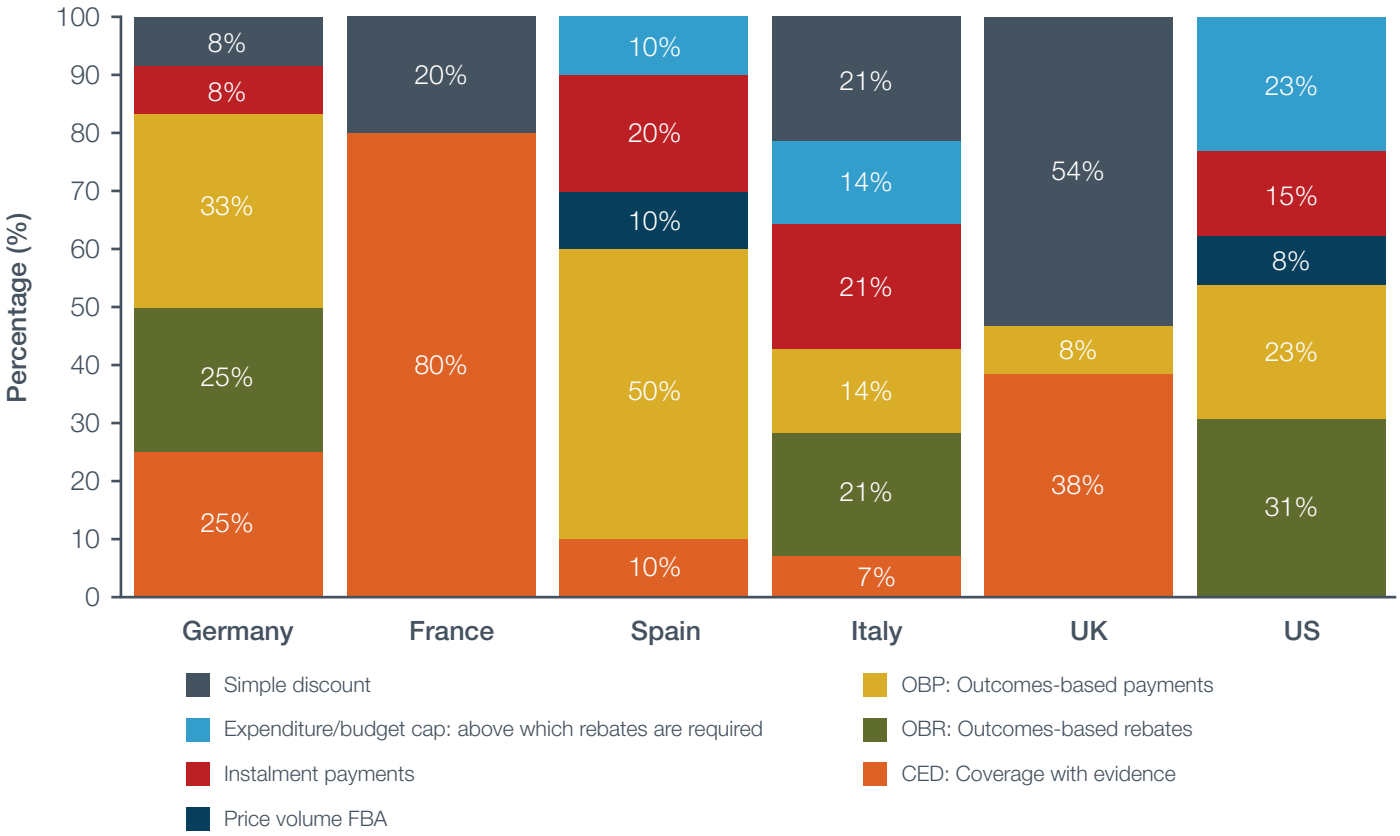
Table 4: An Overview of the Different Types of MEAs and Their Associated Benefits and Challenges

MEA	Description	Payer benefits	Challenges
Simple discount and rebates	Often confidential. Reduce list price to an acceptable value.	Simple and fastest route to market.	Blunt and relatively inflexible instrument.
Budget cap	Maximum budget impact for a product beyond which central rebates apply.	Reduces budget impact uncertainty.	Potentially punishes innovation through industry rebate paybacks.
Price/volume agreement	Price agreed for set volume of patients and reductions based on number of additional patients.	Predictable budget impact.	Impacted by affordability instead of product value.
Instalment or annuity payments	Costs spread over time or multiple financial years.	Reduces risk with upfront payment.	Legislative barriers can prevent staggered payments due to reporting and accounting rules.
‘Netflix’ subscription model	Lump-sum payment to manufacturers for unlimited access to therapy for determined period.	Predictable manufacturer revenues and payer budget impact.	Requires accurate tracking of product use. Complex reimbursement criteria involved.
Population-level coverage-with-evidence (CED)	Addresses clinical and financial uncertainty through real-world-evidence.	Manages uncertainty via real-world evidence.	Risk of overpaying upfront. Increased health technology assessment workload.
Outcomes-based rebate agreement	Upfront payment followed by manufacturer giving discounts (or rebates) if product does not meet expectations.	Shares risk of treatment failure with manufacturer.	High administrative burden on both healthcare professionals and patients to report and track outcomes. Requires advanced data infrastructure.
Outcomes-based payment by result	Manufacturer receives payment upon patient demonstration of agreed outcome within the defined period.		

Finance-based agreement
Performance-based agreement

Cogentia has analysed the use of MEAs for 17 approved gene therapies (*in vivo* and *ex vivo*) and five approved CAR-Ts across the EU4, UK and US. Findings demonstrate regional trends in the use of different MEA archetypes to date (Figure 4).

Figure 4: Gene Therapy and CAR-T MEA Models in the EU4, UK and US



Products considered in this analysis are: Hemgenix, Zolgensma, Luxturna, Imlygic, Vyjuvek, Roctavian, Upstaza, Strimvelis, Libmeldy, Zynteglo, Kymriah, Abecma, Breyanzi, Tecartus, Yescarta, Lyfgenia and Casgevy.

The UK's approach to gene therapy reimbursement has been heavily reliant on simple discount patient access schemes, while others such as the US, Spain and Italy show a greater diversity of MEAs as well as a reliance on outcomes-based schemes (Figure 4). This is reflective of disparities in healthcare systems. The UK's health technology assessment (HTA) body NICE and National Health Service England have a strong preference for simplicity and flexibility, which has thus far manifested in an aversion for complicated agreements and a preference for simple MEA-like discounts.

In contrast, Spain and Italy have both historically had a reputation for implementing outcomes-based agreements, which can be credited in part to the presence of national level infrastructure platforms used to collect the patient data that underpin outcomes-based agreements. Italy has an extensive national system of online registries that date back to 2005 when the Agenzia Italiana del Farmaco (AIFA; Italian Medicines Agency) began to develop them (43). Indeed, AIFA recently showed renewed interest in greater use of MEAs to manage uncertainty having updated the procedure for tracking refunds on such deals. Spain is comparatively newer to MEAs, having negotiated its first MEA in 2010 but recently accelerated its potential for such agreements with the implementation of the VALTERMED platform in 2019 to collect patient data on a national level (44).

Outcomes-based agreements also dominate the gene therapy MEA landscape in Germany. Indeed, CSL Behring recently negotiated a novel prospective cohort outcomes-based contract for Hemgenix for haemophilia B that enables future reimbursement to be adjusted based on outcomes. The contract also included annual rates on a limited period of time to statutory payers as “an adaptive, annual, performance-based payment model” that is “particularly suitable for the German healthcare system”, CSL Behring said in a statement (45). This contract relies on annual payments, as opposed to a single upfront payment, that are only paid in cases of success.

GENE THERAPY HTA LANDSCAPE IN THE EU4 AND UK

Overall, the reimbursement landscape of gene therapies has rapidly expanded in recent years and the use of MEAs could be hypothesised to continue to feature in their access. Table 5 provides an overview of HTA decisions to date in the EU4 and UK.

Table 5: HTA Outcomes for Select Gene Therapies in the EU4, UK and US

		Reimbursement status					
Brand name	Generic name	DE	FR	SP	IT	UK	US
Beqvez	Fidanacogene elaparvovec-dzkt						CED
Casgevy (SCD)	Exagamglogene autotemcel	CED				CED	MEA
Casgevy (TDT)	Exagamglogene autotemcel	*				CED	MEA
Hemgenix	Etranacogene dezaparvovec	CED		MEA		CED*	CED*
Roctavian	Valoctocogene roxaparvovec	CED			CED		CED*
Upstaza	Eladocagene exuparvovec		*				
Libmeldy	Atidarsagene autotemcel						*
Zolgensma	Onasemnogene abeparvovec	*	*	MEA	*	MEA*	*
Luxturna	Voretigene neparvovec			MEA		MEA	
Strimvelis	Autologous CD34+ enriched cells				MEA		
Imlygic	Talimogene laherparepvec					MEA*	*

**Positive recommendation with restricted indication.*
MEA, managed-entry agreement.
CED, coverage-with-evidence agreement.

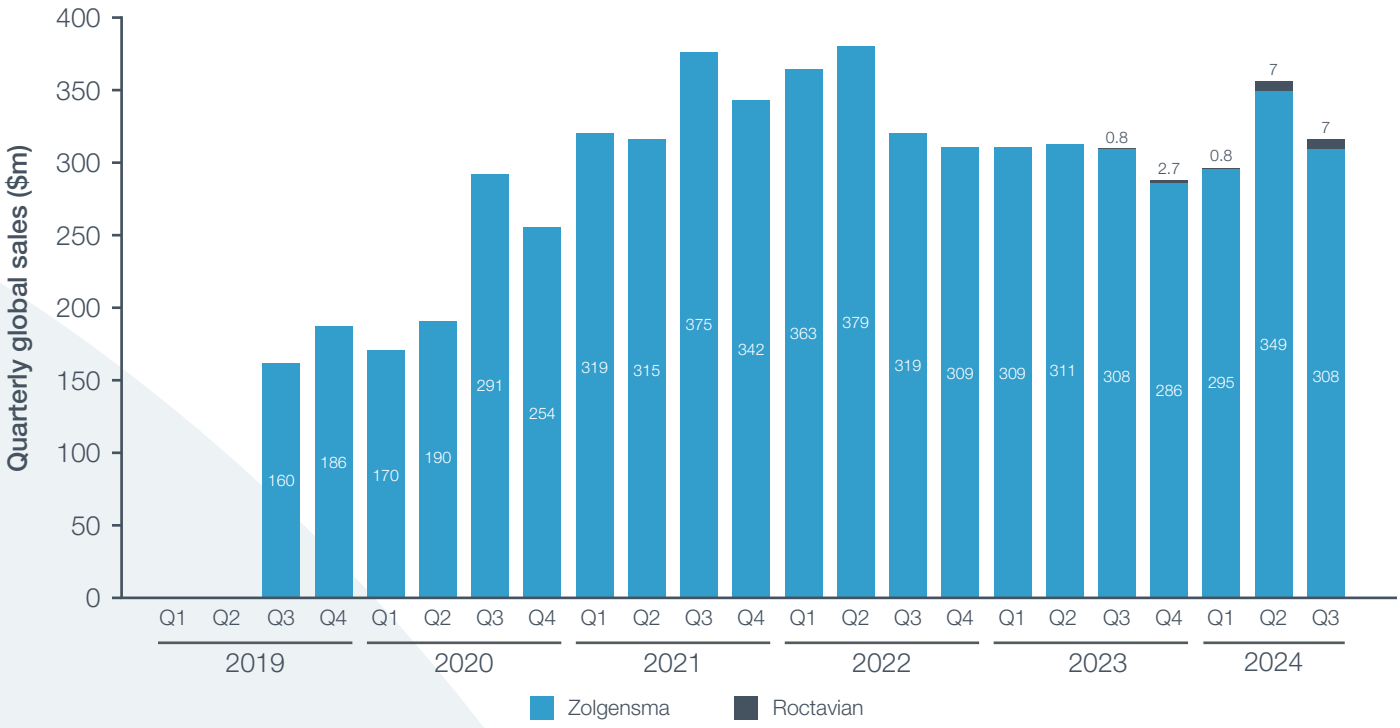
Recommended
Not recommended / agreement not reached
N/A, pending or no assessment

ACCESS HURDLES REMAIN TODAY FOR GENE THERAPIES

Despite novel payment mechanisms, gene therapies still face many reimbursement and access challenges today.

BioMarin's Roctavian for haemophilia A is one of the latest gene therapies to struggle with uptake challenges. Roctavian was supposed to be a triumph, the gene therapy is indicated for a disease with a high unmet need and a high-cost standard of care with factor VIII replacement's annual cost between $300 and $500k per patient. Therefore, Roctavian's price of $2.9 million per one-time dose could still offer significant cost savings should the therapeutic effect be sustained over a patient's life. However, despite BioMarin's commercial hopes for the gene therapy and having originally forecasted $100 million to $200 million in net product revenue in 2023, reality has proven very different (46). Roctavian's actual cumulative sales for 2023 were just $3.5 million, a drop in the ocean compared with Zolgensma's launch success (Figure 5) (47).

Figure 5: Quarterly Sales for Zolgensma vs Roctavian



Source: data from company financial reports

On a conference call, BioMarin CEO Alexander Hardy went through the "complexity" of getting patients on Roctavian treatment:

"We need a motivated patient, supportive payer and a treatment site with a physician who is willing to use the product (45)"

Roctavian's struggling sales can be attributed to limited patient uptake driven by patient hesitancy to receive a novel gene therapy. Furthermore, delays in market access and reimbursement decisions relating to pricing concerns, and the need for specialist infusion sites and healthcare provider administration training have also contributed to Roctavian's struggling uptake to date. Considering Roctavian's stagnant sales, BioMarin announced in April 2024 it was considering the asset's divestment alongside the preferred option to establish the opportunity. BioMarin eventually decided to limit Roctavian's commercialisation to three core markets: the US, Germany and Italy.

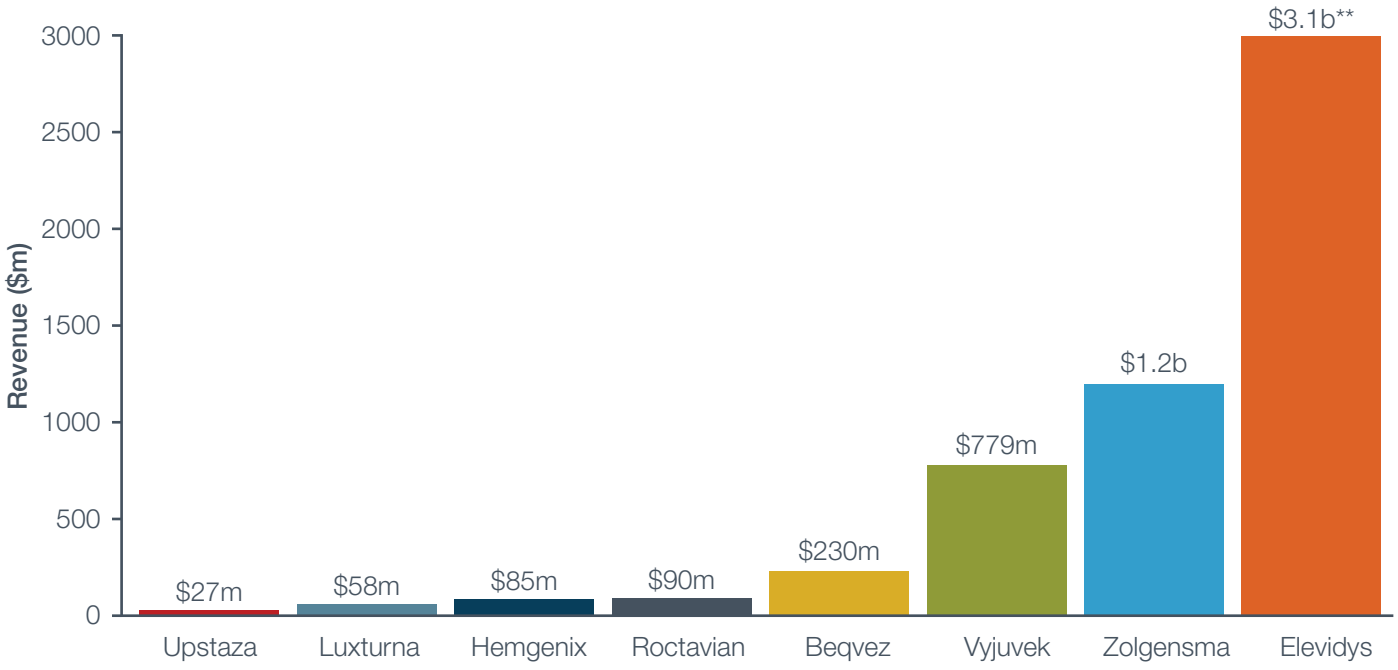
A RECENT MIGRATION TOWARDS MORE PREVALENT DISEASES

While haemophilia A is designated an orphan disease by the EMA (with a prevalence of 0.7 in 10,000 and an estimated 36,000 people with the disease in Europe) it is a larger patient pool than previous gene therapies have traditionally targeted (48). In fact, haemophilia A is likely more than a ten-fold increase in magnitude compared with the eligible patient populations served by some of the first gene therapies such as Glybera and Strimvelis.

A report by Oliver Wyman observed a trend towards addressing broader patient populations, as a result of an expansion into new therapeutic areas (49).

Recent approvals such as Roctavian for haemophilia A, Elevidys for DMD and Casgevy for sickle cell disease, all target diseases with prevalences around 1 in 5,000 (49). Elevidys was the world's first gene therapy for DMD, one of the most frequent genetic conditions affecting approximately 1 in 3,500 male births worldwide (7). In February 2024, the FDA accepted an efficacy supplement to expand Elevidys' indication by removing age and ambulation restrictions; thereby further widening the target patient population (5). Sarepta reports a strong launch for Elevidys that seemingly outperforms even Zolgensma's launch in terms of US revenue generated in the first 30 months (Figure 6) (9).

Figure 6: US Revenue in the First 30 Months of Launch*



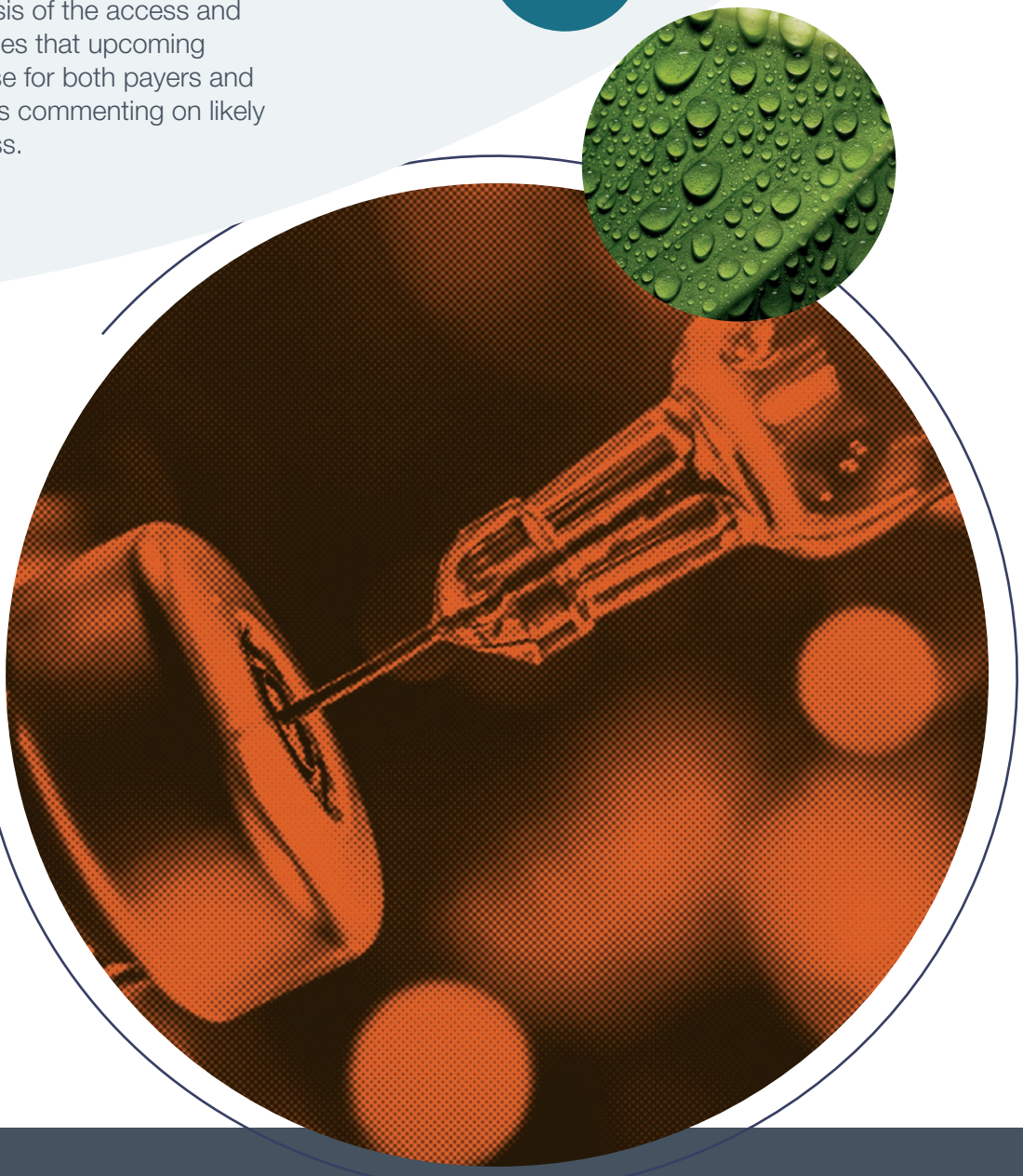
Source: Sarepta company presentation (50)

**US 30-month revenue figures from launch include a combination of actuals, forecasts and consensus estimates.*

***To complete first 30 months, the last four quarters are forward-looking projections based upon external guidance.*

While this exemplifies a recent shift towards more common disorders compared with ultra-rare diseases, it is important to note that the eligible patient populations for these therapies remain relatively small due to restricting genetic and clinical criteria. The trend for gene therapies to target more prevalent conditions could present new challenges for healthcare systems, particularly in terms of cost management and treatment access. Payers and HTA bodies are likely to face increased pressure to develop innovative reimbursement models and value assessment frameworks to address the potential budget impact of these high-cost therapies reaching larger patient groups.

The next chapter of this whitepaper will explore the gene therapy pipeline; providing a forward-looking analysis of the access and reimbursement challenges that upcoming gene therapies may pose for both payers and manufacturers as well as commenting on likely opportunities for success.



CHAPTER 2: THE PIPELINE AND FUTURE OF CELL AND GENE THERAPIES

This chapter aims to provide a forward-looking perspective on the gene therapy clinical pipeline and its potential impact on access and reimbursement challenges. It will explore possible solutions to these challenges and discuss commercially attractive targets for future development. The chapter will also examine how emerging trends, such as the expansion into larger indications and the advent of new technologies like gene editing, may reshape the gene therapy treatment landscape. Additionally, it will present a commercial attractiveness matrix and conduct a budget impact assessment to offer a comprehensive view of the evolving gene therapy market.

Table 10 (Appendix 1) shows the pipeline captured as of January 2025. Key trends in the pipeline are presented below.

THE GENE THERAPY PIPELINE GREW IN 2024

According to a recent report, between Q1 and Q4 2024 the only pipeline stage to see a decline in gene therapy numbers was preclinical development with a 7% decrease since Q1 2024 (Figure 7). As clinical trials progress from phase 1 to phase 3, the number of drug candidates decreases. This reduction occurs because each successive phase presents higher risks and more stringent requirements. Consequently, only a small fraction of the initial drug candidates successfully complete all phases and reach the pre-registration stage. Our pipeline sample followed the same trend (Figure 8).

Figure 7: CGT Pipeline (Q1 2023-Q4 2024)

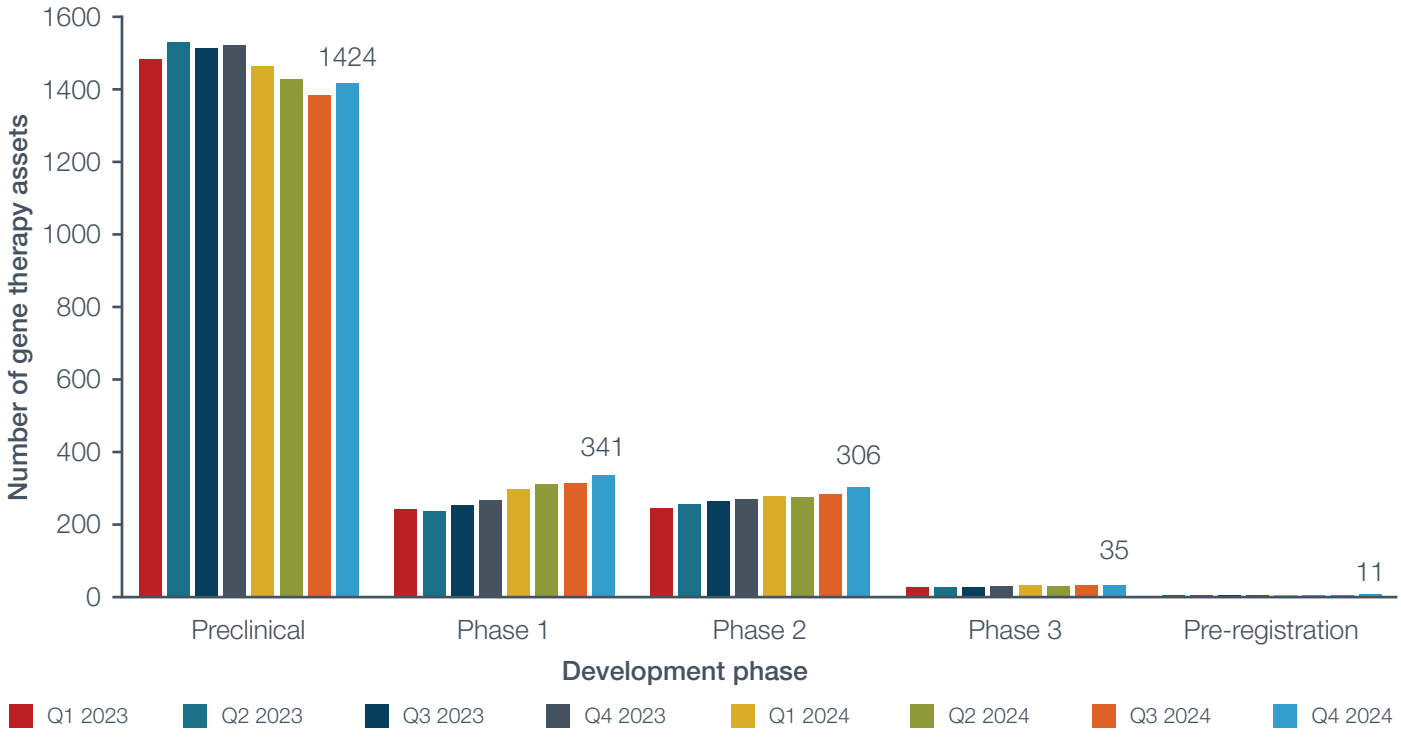
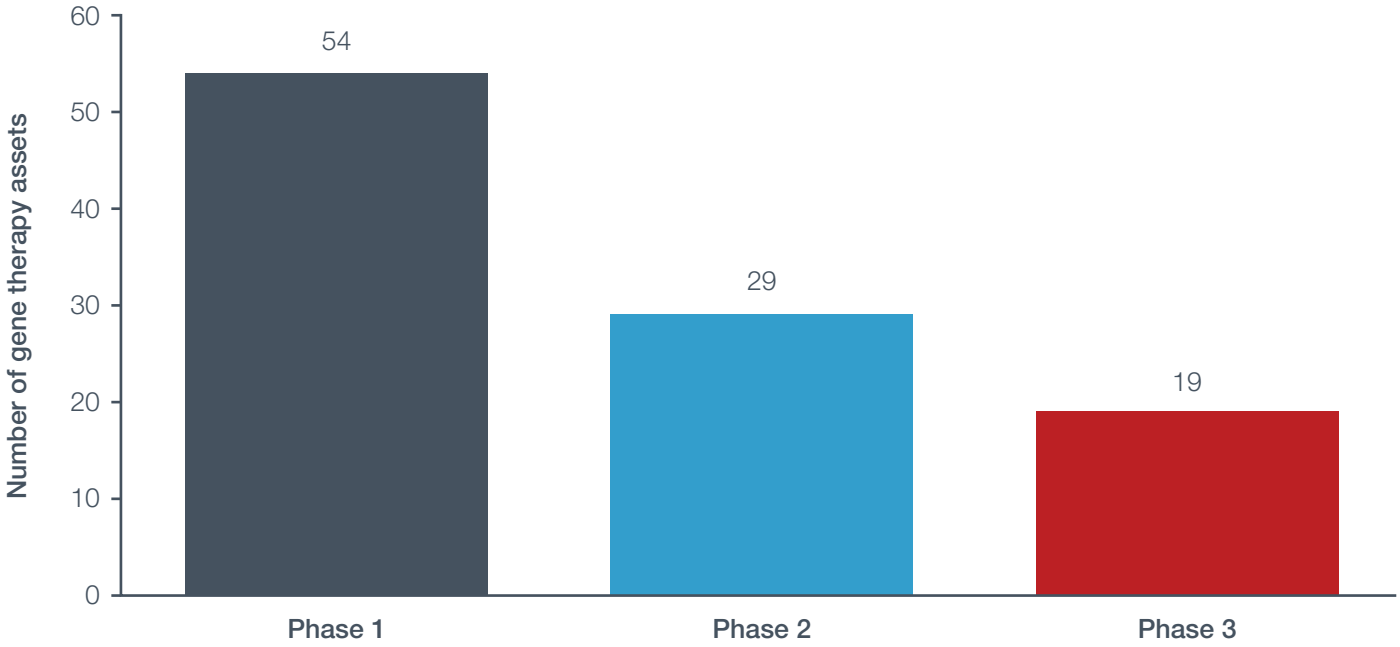


Figure 8: Sampled Gene Therapy Pipeline by Development Phase*

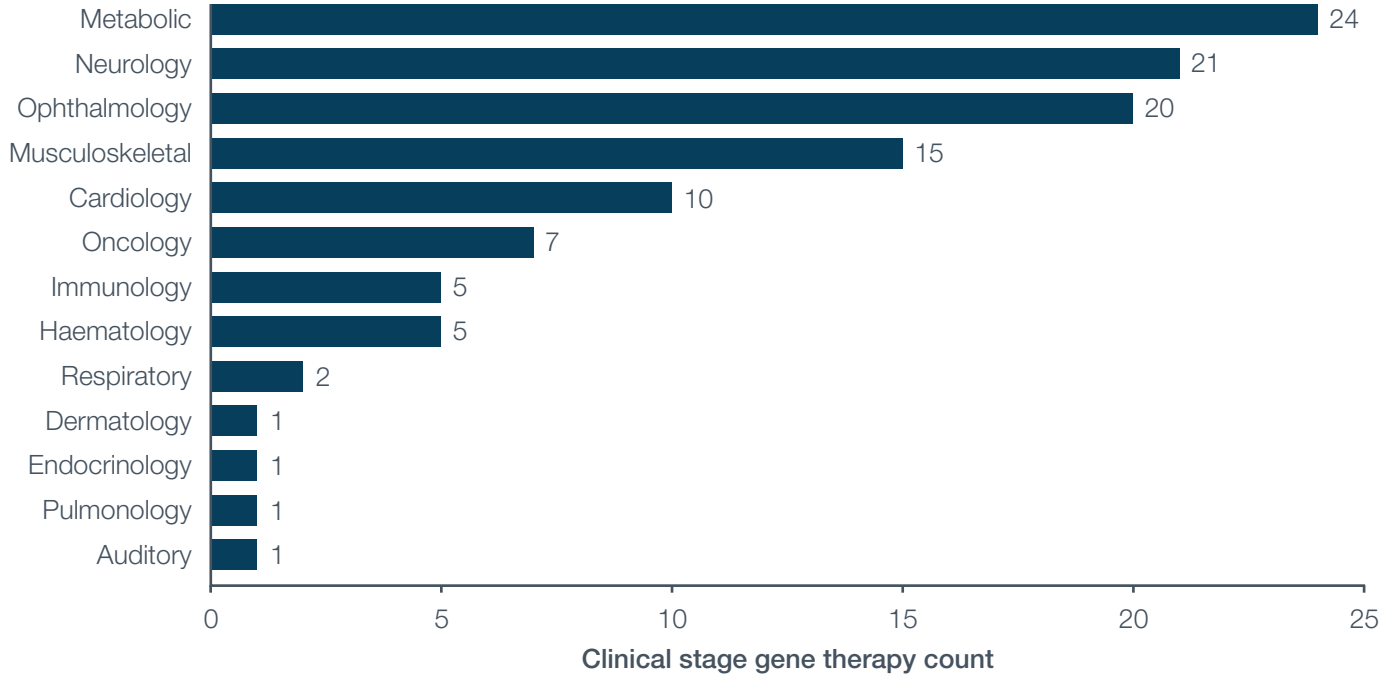


**Gene therapy here refers to in vivo gene replacement therapies and thus CAR-Ts and gene editing assets were not included in our sampled pipeline.*

METABOLIC DISORDERS ARE THE MOST TARGETED INDICATION BY CLINICAL STAGE GENE THERAPIES

According to our analysis, metabolic disorders were the most targeted indication by clinical stage gene therapies, with ~21% of gene therapies in our pipeline targeting these disorders (Figure 9). Neurological- and ophthalmology-based diseases were the second and third most common types of diseases in the pipeline.

Figure 9: Targeted Indications by Clinical Stage Gene Therapies



Inherited metabolic diseases are rare genetic disorders that often result in severe and disabling symptoms. These conditions typically have limited treatment options, making them challenging to manage effectively.

One example is Ultragenyx's DTX301 (avalotcagene ontaparvovec), a phase 3 asset for ornithine transcarbamylase (OTC) deficiency. OTC deficiency is the most common urea cycle disorder and is caused by a genetic defect in a liver enzyme responsible for the detoxification of ammonia. Ammonia is a potent neurotoxin, and slight elevations can lead to neurological and cognitive signs and symptoms. Prolonged elevations in ammonia can lead to a metabolic crisis with progressive and irreversible neurocognitive damage with each crisis (51).

Ultragenyx estimate ~10,000 people in their commercially accessible geographies have an OTC deficiency. Approved therapies for OTC must be taken multiple times a day for the patient's entire life and do not eliminate the risk of future metabolic crises. Currently, the only curative approach for OTC is liver transplantation (52).

Metabolic diseases could be the most common indication in the clinical stage gene therapy pipeline due to a combination of factors. Their monogenic nature makes them ideal targets for gene therapy, while the high unmet medical need and limited existing treatment options create a significant opportunity for intervention. The liver's central role in metabolism and the success of liver-targeted gene therapies in preclinical models further enhance their appeal. Additionally, recent technological advancements, regulatory support for rare disease treatments, and the potential for long-term efficacy make metabolic disorders particularly attractive for gene therapy development. These factors, coupled with the diverse pipeline of metabolic diseases currently being targeted, likely contribute to their prevalence in clinical stage gene therapy trials (53).

THERE IS A TREND FOR GENE THERAPIES TO TARGET MORE PREVALENT DISEASES

Our analysis shows 29.2% of clinical stage gene therapy assets were indicated for prevalent diseases (defined as disorders affecting >5 in 100,000 people) as of January 2025 (Figure 10). This is a 14.2% increase from our previous analysis in 2021 (Figure 10). Supporting this trend, the Alliance for Regenerative Medicine noted the same trend with several gene therapies targeting more prevalent diseases in the pipeline such as wet age-related macular degeneration (AMD), Parkinson's disease, multiple sclerosis and type 1 diabetes are on the horizon (Table 6).

Figure 10: The Prevalence of Indication Types in the Gene Therapy Clinical Pipeline in 2021 vs Q1 2025

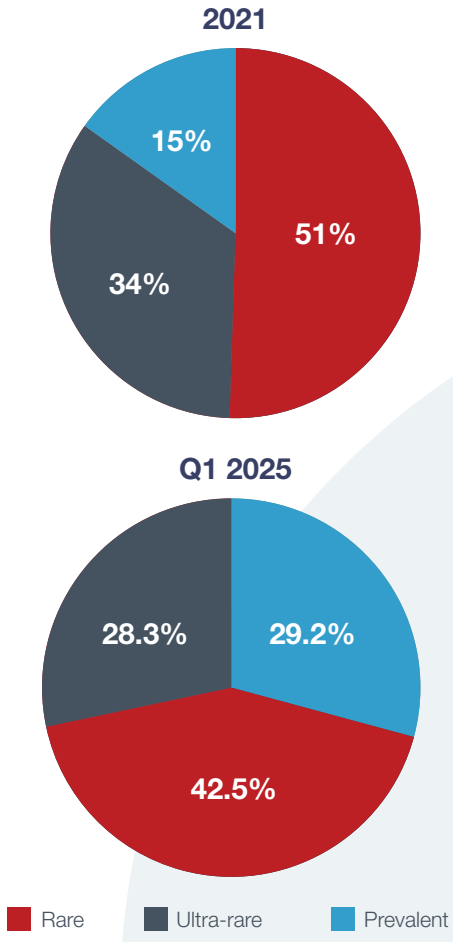


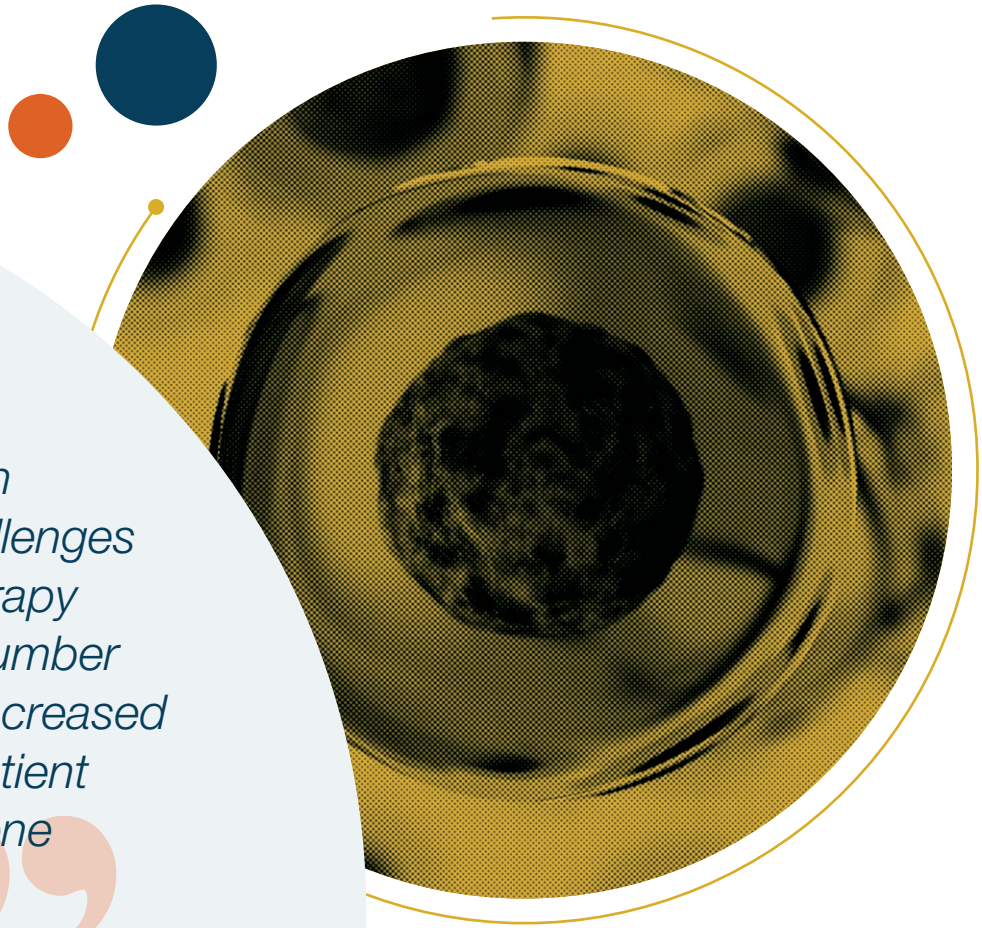
Table 6: Prevalent Disease Breakthroughs Are Coming

Multiple sclerosis	Type 1 diabetes	Wet AMD	Parkinson's disease
1.5 million patients in the US, EU and Japan	3.8 million patients in the US, EU and select geographies	5.7 million patients in US, EU and Japan	10 million patients worldwide
Phase 2 Kyverna	Phase 1/2 Vertex and Sana Biotechnology	Phase 3 Regenxbio and AbbVie	Phase 3 Bluerock and Bayer

Source: (54)

Bluerock and Bayer have recently announced their intention to skip from phase 1 to phase 3 for the development of their Parkinson's disease cell therapy Bemdaneprocel. This follows completion and discussion of phase 1 trial data with the FDA under Regenerative Medicine Advanced Therapy designation. The registrational trial, named exPDite-2, is expected to begin in the first half of 2025 and will represent a significant milestone in the development of allogeneic cell-based therapies for neurodegenerative disorders (55).

Gene therapies are increasingly targeting more prevalent diseases due to several key factors. Technological advancements and improved understanding of genetic mechanisms have expanded the scope of gene therapy applications beyond rare monogenic disorders (56). Furthermore, the potential for widespread impact on global health outcomes is significant, as evidenced by therapies targeting common conditions like haemophilia, which affects over one million people worldwide. Economic considerations also play a role, with successful gene therapies for prevalent diseases potentially capable of reducing long-term healthcare costs associated with chronic conditions (57).



The future of cell and gene therapies

Looking forward, we can anticipate two main challenges to the cell and gene therapy landscape, the higher number of therapies... and the increased size of their indicated patient populations. Cell and gene therapy challenge (44)

COMMERCIAL ATTRACTIVENESS MATRIX OF UPCOMING GENE THERAPIES

A commercial attractiveness matrix was developed for ten indications with late-stage gene therapy assets in development. Factors influencing market success were analysed and graded to provide a visual overview of likely commercial impact. This matrix could be used as a tool to predict commercial viability of target disease areas as well as anticipate likely obstacles should these assets reach the market.

The ten disease areas to be assessed:

1. Fanconi anaemia subtype A
2. Leber's hereditary optic neuropathy (LHON)
3. Duchenne muscular dystrophy (DMD)
4. Severe haemophilia A
5. Fabry disease
6. Sanfilippo syndrome type A (MPS IIIA)
7. Parkinson's disease
8. Wet age-related macular degeneration (AMD)
9. Gaucher disease
10. X-linked retinitis pigmentosa

From a purely commercial standpoint, a target disease should have the following characteristics:

- **Prevalence:** the disease should be relatively prevalent in rare disease terms, but not so prevalent that payers baulk at a price anywhere above five figures. A prevalence of around 1/10,000 appears optimal (e.g. SMA type 1 allows Zolgensma to command a high price while still treating a steady stream of patients).
- **Age of eligibility:** the gene therapy should be administered as early in life as possible, with the potential for benefits to accrue over a full lifetime.
- **Disease burden:** the disease should be severely debilitating, or the gene therapy should be targeted at the most severe form of the disease (e.g. Sanfilippo syndrome type A or SMA type 1).
- **Healthcare resource use:** resource use should be high with significant cost savings expected in those who receive a gene therapy.
- **Current treatment options:** options should be limited and not considered to be effective, potentially with challenging safety profiles and questions over benefit: risk ratio.
- **Cost of comparator:** comparators should be expensive, setting a precedent for high pricing and offering a simple like-for-like cost offset for budget impact estimates.
- **High price precedent:** high price precedents among analogues support favourable pricing scenarios.

Table 7: Comparison of Gene Therapy Targeted Disease Areas Based on Cogentia's Commercial Predictors of Success Matrix

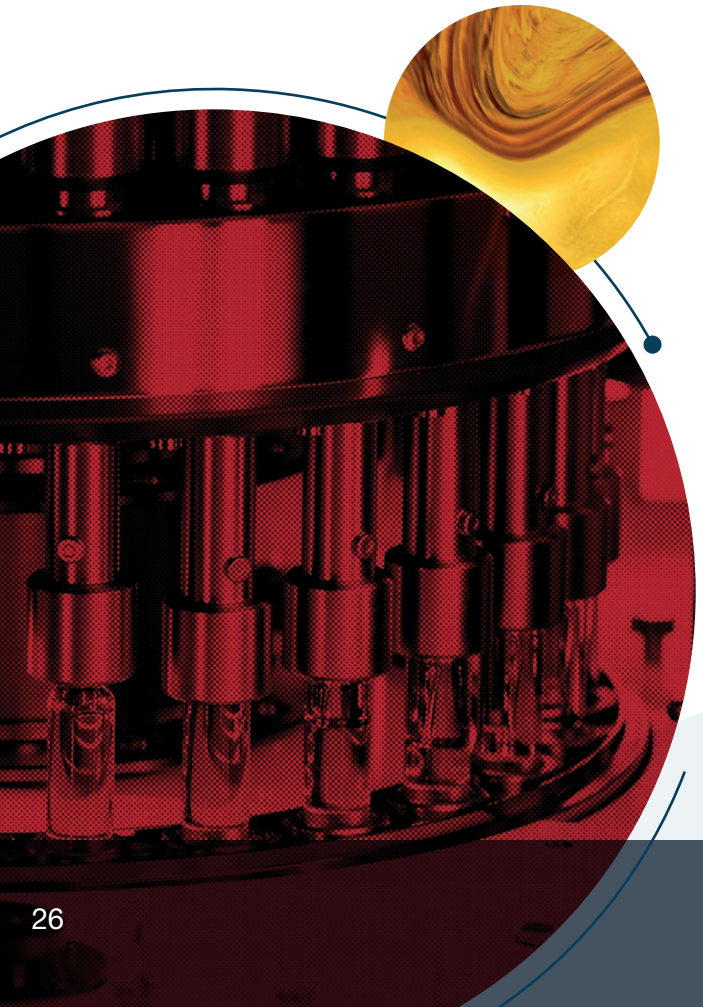
Example asset	Disease area	Prevalence	Age (yrs)*	Disease burden	Direct treatment costs	Current treatment options	Cost of comparator per patient per year*	High price precedent?
RPL102	Fanconi anaemia subtype A	1-5/1,000,000	3-7	Characterised by physical abnormalities, bone marrow failure and increased risk for malignancy.	$80k- $200k per year for HSCT	HSCT, androgens	$80k-$200k for HSCT	Somewhat
Lumevoq	LHON	>10/100,000	15-17	LHON typically initiates painlessly in one eye, progressing to the second eye within a year, leading to profound visual impairment, colour vision deficits and central scotomas.	€80k with Raxone treatment + BSC vision aids (Europe)	Raxone, BST. No approved treatment in US	€80k	N
RGX-202	DMD	5/100,000	4-7	Rapidly progressive, lethal neuromuscular disorder. Life expectancy <30 years.	Ranging from $10k-$80k per year as disease progresses	Corticosteroid, Translarna, Exondys 51, Vyondys 53, Elevidys	$300k -$1m $3.2m (Elevidys)	
Giroctocogene fitelparvovec	Severe haemophilia A	5/100,000	18+	Life expectancy around normal with extensive treatments.	BioMarin put the cost of lifetime treatment at $25m (US costs)	Factor VIII, Hemlibra Roctavian	$400k- $700k $2.9m	Y
Isaralgagene civaparvovec	Fabry disease	10/100,000	16-50	Type 1 leads to excruciating pain in extremities and progressive renal insufficiency. Life expectancy 58-75 years.	~$60k per year, including hospital admissions, surgery, diagnostic imaging, ERT	Fabrazyme, Galafold, Elfabrio	$200k- $400k	Y
UX111	Sanfilippo syndrome type A (MPS IIIA)	1/100,000	0-2	Significant developmental delay + cognitive decline. Life expectancy <15 years.	Poorly recorded, likely to be well over $100k per year in severe disease	No approved treatment	N/A	N
Bemdaneprocel	Parkinson's disease	10 million worldwide	30-75	Symptoms include uncontrollable tremors, bradykinesia, deteriorating cognitive function.	$30-$60k per year. Includes hospital inpatient + outpatient appts, non-acute institutional care	Carbidopa-levidopa, deep brain stimulation	$40-50k	N
ABBV-RGX-314	Wet AMD	~6 million worldwide	50-85	Rapid and severe central vision loss. Most people move from diagnosis to legal blindness in 10 years.	$10-$20k per year, including diagnostic and assistance with daily activities	Eylea Lucentis	$25k per eye	N
FLT201	Gaucher disease	>1/100,000	20-40	Shortened life expectancy. Bone pain, reduced lung function, anaemia and thrombocytopenia.	>$200k per year	ERTs; Cerezyme, VPRIV, Elelyso. SRTs; Zavesca, Cerdelga	Cerezyme: $200k-$300k per year	Y
Bota-vec	X-linked retinitis pigmentosa	~3/100,000 males	40	Gradual loss of peripheral vision which results in progressively worsening 'tunnel vision'. Most patients are legally blind by the age of 40.	In the absence of available treatments, direct healthcare costs are low for people with XLRP	No effective treatments	N/A	N

**Age in clinical trials. Ratings relate to impact on likelihood of positive P&R and commercialisation. Ratings span dark green ▬ (highly favourable) to red ▬ (likely to prove challenging). As an example, a treatment for a disease with a reasonable prevalence, early treatment with potential to accrue a lifetime of benefits, high disease burden, large cost offsets in resource use and comparator, and a successful analogue is well set for success. All comparisons are relative and based on subjective assessment. Other reviewers may come to different conclusions. Disease burden based on more severe forms of disease, where gene therapies would be used. Costs of comparators based on US prices. Scores are assigned to each disease area using colour coding with dark green ▬ (worth 4 points), mid-green ▬ worth (3 points), light green ▬ (2 points), yellow ▬ (1 point) and red ▬ (0 points). BSC, best supportive care; ERT, enzyme replacement therapies; HSCT, haematopoietic stem cell transplant; P&R, pricing and reimbursement; SRT, substrate reduction therapy. Assessment based on Cogentia review of published sources. Disease prevalence taken from Orphanet, with the exception of Parkinson's disease and wet AMD. Other costs and descriptive text based on analysis of public sources.*

Table 8: Ranking of Commercial Attractiveness of Gene Therapy Based on Targeted Disease Areas

Disease area	Prevalence	Age (yrs)*	Disease burden	Direct treatment costs	Current treatment options	Cost of comparator/ year	Successful analogue?	Average
Sanfilippo syndrome type A (MPS IIIA)	4	3	4	4	4	4	0	3.3
DMD	3	3	4	2	2	4	4	3.1
Fanconi anaemia subtype A	0	4	4	4	4	3	1	2.9
Gaucher disease	0	3	3	4	0	4	4	2.6
Severe haemophilia A	3	1	1	4	1	4	4	2.6
Fabry disease	4	1	3	2	1	3	4	2.6
LHON	3	3	2	3	3	2	0	2.3
X-linked retinitis pigmentosa	1	1	2	0	4	4	0	1.7
Parkinson's disease	0	0	3	2	2	0	0	1.0
Wet AMD	0	0	2	0	0	0	0	0.3

All comparisons are relative and based on subjective assessment. Other reviewers may come to different conclusions. Scores assigned to each disease area using the colour coding seen in Table 5, with dark green worth 4 points, mid-green worth 3 points, light green 2 points, yellow 1 point and red 0 points.



By using the matrix displayed in Table 7, we can start to assess what challenges manufacturers may face based on the disease areas being targeted in the current gene therapy pipeline, as well as look at disease areas that tick a lot of boxes commercially. Table 8 shows that the ten disease areas assessed display a high degree of heterogeneity, scoring a wide range from 0.3/4 to 3.3/4 on the predictive factors laid out above.

Next, we provide more detail into three of these disease areas, selecting one disease area that ranks at the top in terms of commercial attractiveness, one in the middle and one towards the bottom for a contrasting view (Table 8).

SANFILIPPO SYNDROME TYPE A (MPS IIIA)

According to our matrix, Sanfilippo syndrome appears promising from a commercial viability perspective. UX111 is a gene therapy being developed by Ultragenyx Pharmaceutical for Sanfilippo syndrome type A. In January 2025, Ultragenyx submitted a biologics licence application to the FDA seeking accelerated approval of UX111. If approved, UX111 would become the first therapy to be cleared in the US for Sanfilippo syndrome, a rare childhood form of dementia (58).

Patients would receive the gene therapy at age 0-2 years (the median age of children treated in the UX111 phase 1/2/3 trial was 21.8 months), and thereafter potentially accrue a lifetime of benefits (59). Sanfillipo syndrome poses a significant burden as a rapidly progressive disease that often leaves patients unable to walk and speak. Life expectancy typically does not extend beyond 15 years. Current standard of care is primarily focused on symptom management and palliative care, there are no approved disease-specific treatments (60).

Therefore, the unmet need for a curative treatment is significant and there is currently little to price benchmark a prospective gene therapy against.

HAEMOPHILIA A

Both haemophilia A and B have proved hotly contested battlegrounds for prospective gene therapy players with several assets in late-stage development or approved in haemophilia A and B (Table 9).

Table 9: Gene Therapies for Haemophilia in Late-Stage Development

Haemophilia A			
Asset name	Indication	Developer	Phase
Roctavian	Severe haemophilia A	BioMarin	Approved
Giroctocogene fitelparvovec	Severe haemophilia A	Sangamo (previously in development with Pfizer until January 2025)	3
Dirloctocogene samoparvovec (SPK-8011)	Severe or moderately severe haemophilia A	Roche	Discontinued*
Haemophilia B			
Beqvez (Durveqtix)	Moderate - to - severe haemophilia B	Pfizer	Approved
Hemgenix	Severe and moderately severe haemophilia B	UniQure and CSL Behring	Approved

**Roche's spokesperson confirmed the termination of the dirloctocogene samoparvovec (SPK-8011) study and explained that the company is mothballing SPK-8011 as it introduces a new, enhanced function factor VIII (FVIII) haemophilia A candidate to its gene therapy pipeline. "This decision is based on our belief that an enhanced function FVIII variant has the potential to address remaining unmet needs and reduce the treatment burden for patients," the spokesperson explained. "This decision builds on the promising results seen in the phase 1/2 dirloctocogene samoparvovec study, which assessed the safety and efficacy of the factor VIII gene transfer treatment in individuals with haemophilia A, demonstrating favourable safety, durability and predictability using a low-dose approach." Roche has not yet incorporated this new programme into its online pipeline, which was last updated October 23 and still lists SPK-8011. Source: (61)*

Pfizer

We believe it is best to re-dedicate our time and resources to those assets and treatments that will have the greatest impact on patients and the greatest chance of commercial success

Our last gene therapy whitepaper noted haemophilia A could be a challenging target commercially and 4 years on that prediction appears to have come true. As described in the previous chapter, Roctavian's sales are far removed from BioMarin's hopes as challenges with patient hesitancy and reimbursement have stifled uptake. Adding to the bleak picture for gene therapies in haemophilia A, Pfizer withdrew from its partnership with Sangamo for the co-development of giroctocogene fitelparvovec. The move came as a shock to Sangamo after positive phase 3 results had been released.

In statement, Pfizer said "the decision was made following an extensive analysis of clinical trial results, expert feedback and a slow uptake of haemophilia A gene therapy in patients with moderate-to-severe disease and there is currently limited interest in another gene therapy option for the specified patient population" (62). In addition to watching Roctavian's discouraging performance, some speculate it is likely Pfizer's recently approved monoclonal antibody (HYMPAVZI) for haemophilia A and B is anticipated to outperform giroctocogene fitelparvovec in the long term; thus making the justification for further investment in the gene therapy challenging (63).

In the US, HYMPAVZI is the first once-weekly subcutaneous prophylactic treatment for eligible people living with haemophilia B, and the first to be administered via a pre-filled pen or syringe for eligible people living with haemophilia A or B, likely to be a more preferred route of administration by patients (63).

In our matrix, haemophilia A scored 2.6/4 given it is a fairly "common" rare disease with a modest unmet need and high cost of comparators but with the >18 years old administration age and around normal life expectancy with extensive treatment expected to provide challenges. The commercial reality appears somewhat aligned with this assessment, with payers unconvinced by the added benefit and therapeutic need in view of the single-arm pivotal trial and small patient numbers. Indeed, despite national price agreement in Germany, sub-insurers inserted new barriers to access that further impeded access beyond patient hesitancy. While Roctavian's number of infusions are starting to pick up its future remains uncertain, with divestment still an option should sales plateau. As the haemophilia treatment landscape evolves with the introduction of increasingly efficacious and more convenient factor replacement therapies requiring less frequent administration, patients' willingness to undergo gene therapy may decrease. This shift is partly due to many patients being content with their current treatment regimens and expressing caution about gene therapy's potential adverse events and long-term durability.

WET AMD

Along with Parkinson's disease, wet AMD is the obvious outlier in Table 8. A prevalent population of ~6 million globally and an average age of onset around 55 years seems an odd target for a gene therapy (54, 64). With this age of onset, potential benefits from a gene therapy will be realised for 55 years less than for those with Sanfilippo syndrome type A for example. Pricing of comparators is also not excessive, likely owing to the large addressable pool of patients.

ABBV-RGX-314 is being developed as a novel, one-time subretinal treatment that includes the NAV® AAV8 vector containing a gene encoding for a monoclonal antibody fragment. The expressed protein is designed to neutralise VEGF activity, modifying the pathway for formation of new leaky blood vessels and retinal fluid accumulation (65).

AMD is a significant ocular condition that predominantly affects older individuals, particularly in Western nations, where it stands as the leading cause of vision impairment. This disorder manifests in two distinct forms during its advanced stages: the atrophic (dry) variant and the neovascular (wet) variant. Currently, only wet AMD has viable treatment options. Standard of care for wet AMD involves repeated intraocular injections of drugs that inhibit VEGF-A. While this approach can potentially halt disease progression and delay vision loss, it rarely leads to significant visual improvement and does not result in a cure (66).

The eye presents a compelling target for gene therapy due to its unique anatomical and physiological characteristics. Its compact size, compartmentalised structure, and immune-privileged status reduce the risk of systemic exposure and minimise potential immune responses to introduced genetic material.

Advanced non-invasive imaging techniques, such as optical coherence tomography, fundoscopy, angiography and two-photon microscopy, enable real-time monitoring of gene therapy procedures and their safety profiles. Furthermore, the eye's genetic landscape often features conditions where alterations in a single gene can manifest as various clinical presentations. For example, homozygous mutations in the RPE65 gene can result in either Leber congenital amaurosis type 2 or rare forms of retinitis pigmentosa. This genetic simplicity in some ocular disorders facilitates the development of targeted therapies. Collectively, these factors make the eye an ideal organ for exploring and advancing gene therapy techniques, potentially leading to groundbreaking treatments in ophthalmology such as ABBV-RGX-314 (66).

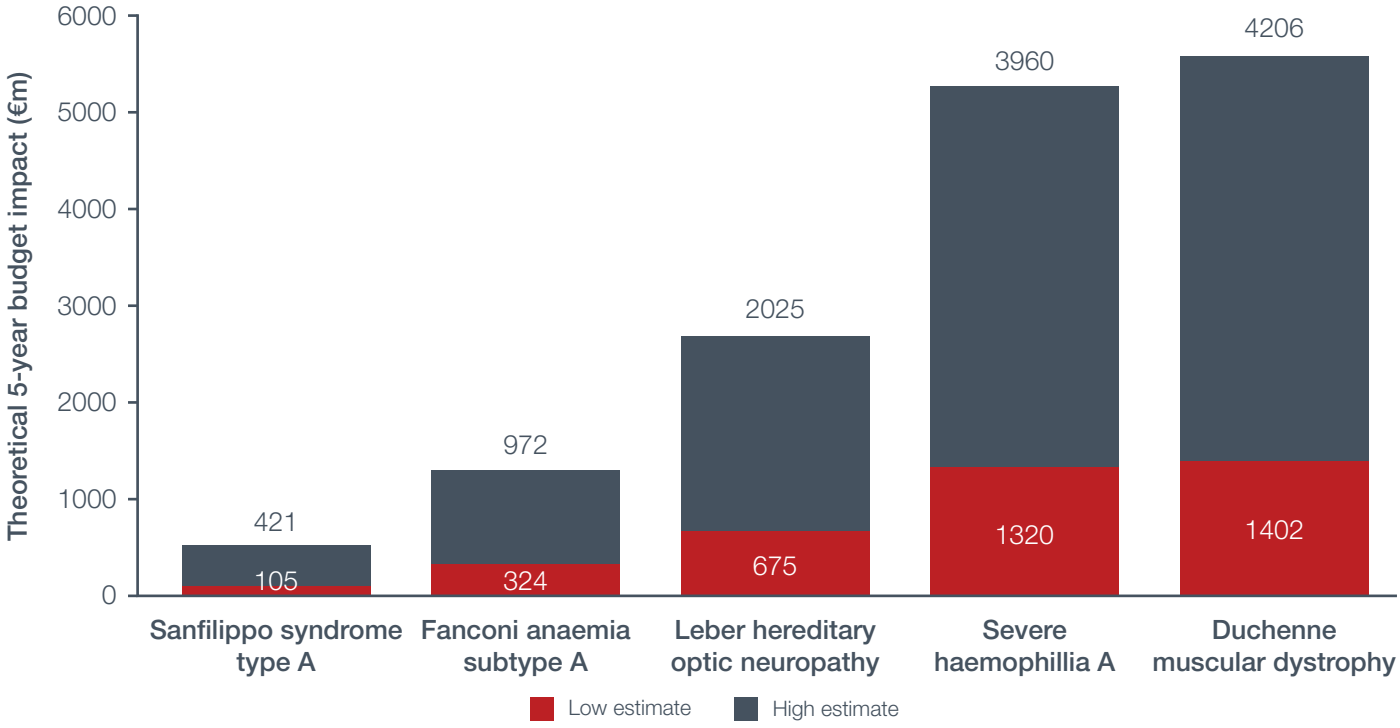
Gene therapies for prevalent diseases present a distinct commercial landscape compared with those for rare conditions. With a larger addressable population and higher incidence rates, these therapies offer more sustained market opportunities, resembling traditional chronic disease treatment models. This environment may allow for multiple market entrants, potentially driving innovation and price competition. The steady stream of newly diagnosed patients ensures a more stable long-term demand curve, avoiding the rapid market depletion seen in rare disease treatments. However, significant challenges remain, including the need for scalable manufacturing processes to meet larger population demands, pricing pressures to ensure affordability for a broader patient base, and the task of convincing payers to cover high upfront costs for larger groups.

BUDGET IMPACT ASSESSMENT

Figure 11 shows the estimated 5-year budget impact of a high-cost gene therapy across five pipeline indications. A high and low budget impact assessment is provided to account for varying assumptions in market share and price. However, gene therapy uptake has often been slow relative to expectations, and so these theoretical budget impacts would not necessarily translate into actual uptake.

Figure 11 illustrates that for more prevalent conditions such as severe haemophilia A and DMD, the budget impact of high-cost gene therapies could be substantial, potentially reaching billions of dollars annually. This presents a significant challenge for payers, who must balance the promise of transformative treatments with financial sustainability. The impact is particularly concerning given the potential for multiple high-cost therapies to enter the market simultaneously, compounding budget pressures.

Figure 11: Theoretical 5-Year European Budget Impact Analysis of Five Gene Therapies in Late-Stage Development



Low market impact assumes of a price of €1 million and 30% market share, while high market impact is based on a price of €2 million and 40% market share for ex vivo and 60% market share for in vivo gene therapies. Estimates are based on the EU eligible patient population pool at 5 years post product launch. All indications shown had one-time administration gene therapies in late-stage development with expected launch date between 2024 and 2026. Indications were selected on the basis that they had one or more gene therapies in late-stage development with the potential to launch in the near term (2024-2026).

Targeting specific subgroups of the eligible population with the highest unmet need is one method to reduce spending alongside price reductions, sales caps and novel financing mechanisms as discussed. Despite these efforts, the cumulative effect of gene therapies for larger patient populations remains a credible concern for healthcare systems striving to maintain comprehensive coverage while managing limited resources.

CONCLUSIONS

This whitepaper provides critical insights into the evolving landscape of gene therapies, revealing a shift towards more prevalent diseases and a growing sense of caution in the industry. The initial excitement surrounding gene therapies has been tempered by real-world challenges, as exemplified by Roctavian's struggling uptake in haemophilia A and Beqvez's struggle in haemophilia B. This analysis highlights the need for nuanced market access strategies across diverse therapeutic areas, with commercial attractiveness scores varying widely from 0.3 in wet AMD to 3.3 out of 4 for Sanfilippo syndrome type A (MPS IIIA). This heterogeneity underscores the importance of thorough market assessment before committing resources.

The case of Roctavian serves as a sobering reminder of the critical need for robust value demonstration and consideration of innovative pricing models to overcome payer scepticism and patient hesitancy. With potential billion-dollar annual budget impacts in prevalent conditions like severe haemophilia A and DMD, proactive engagement with payers is essential to develop sustainable funding solutions. Traditional market access approaches are proving insufficient, necessitating novel strategies such as outcome-based agreements and risk-sharing models to address high upfront costs and demonstrate long-term value. However, such agreements are in their infancy and present challenges such as administration burden and complexity.

For market access professionals, success in this evolving landscape hinges on early planning, cross-functional collaboration, and innovative access solutions that align the transformative potential of gene therapies with healthcare system realities, all while navigating an environment of increased scrutiny and measured expectations.

APPENDIX 1

Table 10: Sampled Active Clinical Stage Gene Therapy* Pipeline as of January 2025

IND	Company	Target disease	Therapy area	Prevalence	Phase
4D-150	4D Molecular	Wet AMD and diabetic macular oedema	Ophthalmology	Prevalent	2
4D-310	4D Molecular	Fabry disease	Metabolic	Rare	1
4D-710	4D Molecular	Cystic fibrosis not modulator amenable	Pulmonology	Prevalent	1/2
ABO-102 (UX111)	Abeona Therapeutics (Ultragenyx)	Sanfilippo syndrome type A	Metabolic	Ultra-rare	3
pz-cel	Abeona Therapeutics	Recessive dystrophic epidermolysis bullosa (RDEB)	Ophthalmology	Rare	3
TSHA-102	Abeona Therapeutics / Taysha Therapies	Rett syndrome	Neurology	Rare	1/2
Ixoberogene soroparvovec	Adverum Biotech	Wet AMD	Ophthalmology	Prevalent	2
LX2006	Adverum Biotech / Lexeo Therapeutics	Friedreich's ataxia	Neurology	Ultra-rare	1
GS030	Adverum / GenSight Biologics	Retinitis pigmentosa	Ophthalmology	Rare	2
AT-GTX-502	Amicus Therapeutics	Batten disease	Neurology	Ultra-rare	1/2
AGTC-501	Applied Genetic Tech (Beacon therapeutics)	X-linked retinitis pigmentosa	Ophthalmology	Rare	2/3
ACT-101 (ACTUS-101)	AskBio (now Bayer)	Pompe disease	Metabolic	Rare	1
AAV-GDNF (AB-1005)	AskBio (now Bayer)	Parkinson's disease	Neurology	Prevalent	2
AB-1005 (AAV2-GDNF-MSA)	AskBio (now Bayer)	Multiple system atrophy (MSA)	Neurology	Rare	1
AB-1003 (LION-101)	AskBio (now Bayer)	Limb girdle muscular dystrophy type (LGMD) 2I/R9	Musculoskeletal	Ultra-rare	1
NAN-101 (AB-1002)	AskBio (now Bayer)	Congestive heart failure	Cardiology	Rare	2
ASP2016	Astellas	Cardiomyopathy associated with Friedreich's ataxia	Cardiology	Ultra-rare	1
AT845	Astellas	Late onset Pompe disease (LOPD)	Metabolic	Rare	1/2
AT132	Astellas	X-linked myotubular myopathy	Musculoskeletal	Ultra-rare	2
ATA-200	Atamyo	LGMD	Musculoskeletal	Ultra-rare	1/2
ATSN-101	Atsena Therapeutics	LCA1	Cardiology	Ultra-rare	1/2
ATSN-201	Atsena Therapeutics	X-linked retinoschisis (XLRS)	Ophthalmology	Prevalent	1/2
AVR-RD-02	AVROBIO	Type 1 Gaucher disease	Metabolic	Rare	1/2
AVR-RD-05	AVROBIO	Hunter syndrome	Neurology	Ultra-rare	1/2
AVR-RD-04	AVROBIO (Sold asset to Novartis)	Cystinosis	Metabolic	Rare	1/2
BS01	Bionic Sight	Retinitis pigmentosa	Ophthalmology	Rare	1/2
BBP-812	Bridgebio	Canavan disease	Neurology	Ultra-rare	1
CAN-2409	Candel Therapeutics	Prostate cancer	Oncology	Prevalent	3
CAN-2409	Candel Therapeutics	Non-small cell lung cancer, pancreatic	Oncology	Prevalent	2
CTx-PDE6b	Coave therapeutics	Retinitis pigmentosa	Ophthalmology	Rare	1/2
OTOF Gene Therapy	Eli Lilly	Sensorineural hearing loss due to mutations in the otoferlin gene	Auditory	Prevalent	2
GBA1 Gene Therapy	Eli Lilly	Parkinson's disease	Neurology	Prevalent	2
GRN Gene Therapy	Eli Lilly	Frontotemporal dementia	Neurology	Prevalent	2
FBX-101	Forge Biologics	Krabbe disease	Neurology	Rare	1/2
FLT201	Freeline Therapeutics (now Spur Therapeutics)	Gaucher disease	Metabolic	Rare	3
AMN (SBT101)	Freeline Therapeutics (now Spur Therapeutics)	Adrenomyeloneuropathy	Neurology	Rare	1/2
Ad5FGF-4	Gene Biotherapeuitcs	Refractory angina	Cardiology	Prevalent	3
HSC Ex vivo	Genethon (Ciemat)	Fanconi anaemia subtype A	Haematology	Ultra-rare	2
HSC Ex vivo	Genethon (Ciemat)	Wiskott-Aldrich syndrome	Immunology	Ultra-rare	3
Lumevoq	GenSight Biologics	LHON	Ophthalmology	Rare	3
E10B	Guangzhou Double Bio-products	Advanced castration-resistant prostate cancer	Oncology	Rare	1
E10A	Guangzhou Double Bio-products	Solid tumours	Oncology	Prevalent	2
Engensis (VM202)	Helixmith	Coronary artery disease	Cardiology	Prevalent	1
Engensis (VM202)	Helixmith	Charcot-Marie-Tooth disease	Musculoskeletal	Rare	1

Table 10 continued

IND	Company	Target disease	Therapy area	Prevalence	Phase
Engensis (VM202)	Helixmith	Amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease)	Musculoskeletal	Rare	2
Engensis (VM202)	Helixmith	Diabetic peripheral neuropathy	Neurology	Prevalent	3
Engensis (VM202)	Helixmith	Diabetic foot ulcers (DFU)	Metabolic	Prevalent	3
Engensis (VM202)	Helixmith	Claudication	Musculoskeletal	Prevalent	2
Botaretigene sparoparvovec (bota-vec)	J&J/MeiraGTX	X-linked retinitis pigmentosa	Ophthalmology	Rare	3
kb-707	Krystal Biotech	Solid tumours	Oncology	Prevalent	1
KB408	Krystal Biotech	Alpha-1 antitrypsin deficiency	Respiratory	Rare	1
KB105	Krystal Biotech	Congenital Ichthyosis	Dermatology	Ultra-rare	1/2
KB407	Krystal Biotech	Cystic fibrosis	Respiratory	Rare	1/2
LX2020	Lexeo Therapeutics	Arrhythmogenic cardiomyopathy	Cardiology	Rare	1/2
LX2006	Lexeo Therapeutics	Friedreich's ataxia cardiomyopathy	Cardiology	Ultra-rare	1/2
LX1001	Lexeo Therapeutics	APOE4-associated Alzheimer's disease	Neurology	Prevalent	1/2
E10A	Marsala Biotech	Head and neck cancer	Oncology	Prevalent	3
AAV-AQP1	MeiraGTx	Sjogren's syndrome	Immunology	Prevalent	1/2
AAV-hAQP1	MeiraGTx	Xerostomia	Immunology	Prevalent	2
AAV-GAD	MeiraGTx	Parkinson's disease	Neurology	Prevalent	2
AAV-CNGA3	MeiraGTx	Achromatopsia	Ophthalmology	Rare	2
AAV-CNGB3	MeiraGTx	Achromatopsia	Ophthalmology	Rare	2
AAV-RPE65	MeiraGTx	Retinal dystrophy	Ophthalmology	Rare	2
MB-107	MustangBio	X-linked severe combined immunodeficiency (SCID)	Immunology	Ultra-rare	1/2
MB-207	MustangBio	X-linked SCID	Immunology	Ultra-rare	1/2
MCO-010	Nanoscope Therapeutics	Stargardt disease	Ophthalmology	Rare	1/2
MCO-010	Nanoscope Therapeutics	Retinal pigmentosa	Ophthalmology	Rare	2/3
OTL-203	Orchard Therapeutics (acquired by Kyowa Kirin)	Mucopolysaccharidosis type I	Metabolic	Ultra-rare	1
PBFT02	Passage Bio	Frontotemporal dementia	Neurology	Prevalent	1/2
Giroctocogene fitelparvovec	Sangamo	Haemophilia A	Haematology	Rare	3
RGX-111	RegenXBio (NOW Nippon shinyaku's asset)	Mucopolysaccharidosis type I	Metabolic	Ultra-rare	1/2
RGX-121	RegenXBio	Mucopolysaccharidosis type II	Metabolic	Ultra-rare	3
RGX-202	RegenXBio	DMD	Musculoskeletal	Rare	2
ABBV-RGX-314	RegenXBio / AbbVie	Wet AMD	Ophthalmology	Prevalent	3
RT-200	Renova Therapeutics	Type 2 diabetes	Metabolic	Prevalent	1
RT-100	Renova Therapeutics	Heart failure	Cardiology	Prevalent	2
NG101	Reyon Pharma / Neuracle Genetics	Wet AMD	Ophthalmology	Prevalent	1/2
VM206RY	Reyon Pharma / Neuracle Genetics	Breast cancer	Oncology	Prevalent	1
VM202RY	Reyon Pharma / Neuracle Genetics	Diabetic peripheral neuropathy (DPN)	Neurology	Prevalent	2
RP-A501	Rocket Pharmaceuticals	Danon disease	Metabolic	Ultra-rare	2
RP-L102	Rocket Pharmaceuticals	Fanconi anaemia	Haematology	Ultra-rare	1/2
RP-L201	Rocket Pharmaceuticals	Severe leukocyte adhesion deficiency-I (LAD-I)	Haematology	Ultra-rare	1/2
RP-L301	Rocket Pharmaceuticals	Pyruvate kinase deficiency	Metabolic	Ultra-rare	2
Isaralgagene civaparvovec	Sangamo Therapeutics	Fabry disease	Metabolic	Rare	2/3
SRD-001	Sardocor Corp	Heart failure with reduced ejection fraction (HFrEF)	Cardiology	Prevalent	1/2
SRD-002	Sardocor Corp	Heart failure with preserved ejection fraction (HFpEF)	Cardiology	Prevalent	1/2
SRD-003	Sardocor Corp	DMD-associated cardiomyopathy	Musculoskeletal	Rare	1/2
SRP-6004	Sarepta Therapeutics	LGMD 2B/R2	Musculoskeletal	Ultra-rare	2
Patidistrogene bexoparvovec (srp-9004)	Sarepta Therapeutics	LGMD	Musculoskeletal	Ultra-rare	3

Table 10 continued

IND	Company	Target disease	Therapy area	Prevalence	Phase
Bidridistrogene xeboparvovec (SRP-9003)	Sarepta Therapeutics	LGMD	Musculoskeletal	Ultra-rare	3
TSHA-118	Taysha Gene Tx	Neuronal ceroid lipofuscinosis type 1 (CLN1) disease	Neurology	Ultra-rare	1
UX701	Ultragenyx	Wilson's disease	Metabolic	Rare	1/2
DTX301	Ultragenyx	Ornithine transcarbamylase deficiency	Metabolic	Rare	3
DTX401	Ultragenyx	Glycogen storage disease	Metabolic	Ultra-rare	3
AMT-130	UniQure	Huntington's disease	Neurology	Prevalent	1/2
AMT-191	UniQure	Fabry disease	Metabolic	Rare	1
AMT-162	UniQure	ALS – SOD1	Musculoskeletal	Rare	1
AMT-260	UniQure	Temporal lobe epilepsy	Neurology	Prevalent	1
VTX-801	Vivet Therapeutics	Wilson's disease	Metabolic	Rare	2
VTX-806	Vivet Therapeutics	Cerebrotendinous xanthomatosis	Metabolic	Rare	1

Only assets that are still in clinical development at the time of writing in January 2025 were included. No cell therapies were included.

REFERENCES

1. Mullard A. 2024 FDA approvals. Nat Rev Drug Discov. 2025;24(2)75-82.
2. American Society of Gene and Cell Therapy. Gene, cell, & RNA therapy landscape report. Q3 2024 quarterly data report. 2024. Available from: https://www.asgct.org/global/documents/asgct-citeline-q3-2024-report.aspx.
3. Young CM, Quinn C, Trusheim MR. Durable cell and gene therapy potential patient and financial impact: US projections of product approvals, patients treated, and product revenues. Drug Discov Today. 2022;27(1):17-30.
4. Lee MK, Seyedmousavi S, Auvity S, Pourroy B, Elleboode V, Kachaner I, et al. Forecasting the potential impact of cell and gene therapies in France: projecting product launches and patients treated. Front Med (Lausanne). 2024;11:1324602.
5. Sarepta Therapeutics. Sarepta Therapeutics announces FDA approval of ELEVIDYS, the first gene therapy to treat Duchenne muscular dystrophy [press release]. 2022.
6. Fidler B. Sarepta prices Duchenne gene therapy at $3.2M. 2023. Available from: https://www.biopharmadive.com/news/sarepta-duchenne-elevidys-price-million-gene-therapy/653720/files/3594/653720.html.
7. NORD. NORD® rare disease database. 2024. Available from: https://rarediseases.org/rare-diseases/duchenne-muscular-dystrophy/files/3592/duchenne-muscular-dystrophy.html.
8. Sarepta Therapeutics. Sarepta Therapeutics announces U.S. FDA acceptance of an efficacy supplement to expand the ELEVIDYS indication [press release]. 2024.
9. Bloomberg. World's most expensive drug is now $4.25 million gene therapy. 2024. Available from: https://www.bloomberg.com/news/articles/2024-03-20/world-s-most-expensive-drug-is-now-4-25-million-gene-therapy.
10. Friedmann T. A brief history of gene therapy. Nat Genet. 1992;2(2):93-8.
11. Wills CA, Drago D, Pietrusko RG. Clinical holds for cell and gene therapy trials: Risks, impact, and lessons learned. Mol Ther Methods Clin Dev. 2023;31:101125.
12. Heuvel R. KPMG. Pathway to success in outcomes-based contracting. 2020.
13. Fitzsimons T, Wydysh N, Mittal V. Health Advances. Gene therapy outlook for the US market into 2024 and beyond. 2024. Available from: https://healthadvances.com/insights/blog/gene-therapy-outlook-for-the-us-market-into-2024-and-beyond.
14. IQVIA. Strengthening pathways for cell and gene therapies: current state and future scenarios. 2024. Available from: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/strengthening-pathways-for-cell-and-gene-therapies
15. Food and Drug Administration. Approved cellular and gene therapy products 2025. Available from: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products.
16. European Medicines Agency. CAT quarterly highlights and approved ATMPs. November 2024. Available from: https://www.ema.europa.eu/en/documents/committee-report/cat-quarterly-highlights-approved-atmps-november-2024_en.pdf.
17. Gonçalves GAR, Paiva RMA. Gene therapy: advances, challenges and perspectives. Einstein (Sao Paulo). 2017;15(3):369-75.
18. Medicines and Healthcare products Regulatory Agency. MHRA authorises world-first gene therapy that aims to cure sickle-cell disease and transfusion-dependent-thalassemia [press release]. 2023.
19. Shah-Neville W. Gene editing sector investment struggles: what's driving the slowdown? 2024. Available from: https://www.labiotech.eu/in-depth/gene-therapy-investment-slowdown/.
20. Hodge C. COVID-19 has benefited investment in the cell and gene therapy sector, say 78% of industry professionals: Informa Connect. 2021. Available from: https://informaconnect.com/covid-19-benefited-investment-cell-gene-therapy/.
21. Cable S, Haddad L, Liggio B, Birnbach D. Roche concludes $4.4 billion acquisition of Spark Therapeutics. 2019. Available from: https://www.goodwinlaw.com/en/news-and-events/news/2019/12/12_17-roche-concludes-acquisition-of-spark.
22. Tome Biosciences. Tome Biosciences acquires Replace Therapeutics [press release]. 2024.
23. AstraZeneca. AstraZeneca completes equity investment agreement with Cellectis [press release]. 2024.
24. Kyowa Kirin, Orchard Therapeutics. Kyowa Kirin successfully completes acquisition of Orchard Therapeutics, a global gene therapy leader for rare diseases [press release]. 2024.
25. Novartis. Addressing unmet needs for inherited neuromuscular diseases [press release]. 2024.
26. Roche. Roche enters into a definitive agreement to acquire Poseida Therapeutics, including cell therapy candidates and related platform technologies [press release]. 2024.
27. Sabatini MT, Chalmers M. The cost of biotech innovation: exploring research and development costs of cell and gene therapies. Pharmaceut Med. 2023;37(5):365-75.
28. Sabatini MT, Xia T, Chalmers M. Pricing and market access challenges in the era of one-time administration cell and gene therapies. Pharmaceut Med. 2022;36(5):265-74.
29. Chancellor D, Barrett D, Nguyen-Jatkoe L, Millington S, Eckhardt F. The state of cell and gene therapy in 2023. Mol Ther. 2023;31(12):3376-88.

30. Valsecchi M. Nature Italy. Rescue of an orphan drug points to a new model for therapies for rare diseases. 2023. Available from: https://www.nature.com/articles/d43978-023-00145-1.
31. Novartis. AveXis receives FDA approval for Zolgensma®, the first and only gene therapy for pediatric patients with spinal muscular atrophy (SMA) [press release]. 2019.
32. European Medicines Agency. EU/3/15/1509 - orphan designation for treatment of spinal muscular atrophy. 2015. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu-3-15-1509.
33. Institute for Clinical and Economic Review. A look at Spinraza and Zolgensma for spinal muscular atrophy. 2019.
34. Stein R. At $2.1 million, new gene therapy is the most expensive drug ever: Health Inc. 2019. Available from: https://www.npr.org/sections/health-shots/2019/05/24/725404168/at-2-125-million-new-gene-therapy-is-the-most-expensive-drug-ever.
35. Institute for Clinical and Economic Review. Spinraza® and Zolgensma® for spinal muscular atrophy: effectiveness and value. 2019. Available from: https://icer.org/wp-content/uploads/2020/10/ICER_SMA_Final_Evidence_Report_052419.pdf.
36. National Institute for Health and Care Excellence. Onasemnogene abeparvovec for treating spinal muscular atrophy. 2023. Available from: https://www.nice.org.uk/guidance/hst15.
37. Liu A. New Zolgensma 'inflection point' is here as Novartis snags EU nod for SMA gene therapy. 2020. Available from: https://www.fiercepharma.com/marketing/new-zolgensma-inflection-point-here-as-novartis-snags-eu-nod-for-sma-gene-therapy.
38. Meglio M. Intrathecal Zolgensma meets primary end point in phase 3 STEER study of spinal muscular atrophy neurology live. 2025. Available from: https://www.neurologylive.com/view/intrathecal-zolgensma-meets-primary-end-point-phase-3-steer-study-spinal-muscular-atrophy.
39. Liu A. After delay with FDA, Novartis touts pivotal trial win for intrathecal Zolgensma in older SMA patients. 2025. Available from: https://www.fiercepharma.com/pharma/after-delay-fda-novartis-touts-pivotal-trial-win-intrathecal-zolgensma-older-sma-patients#:~:text=More%20than%20three%20years%20after,therapy%20a%20much%2Dneeded%20boost.
40. Avery NM. Swissinfo.ch. Whatever happened to the world's most expensive drug? 2023. Available from: https://www.swissinfo.ch/eng/multinational-companies/novartis-switzerland-worlds-most-expensive-drug/75388576.
41. Liu A. Zolgensma's slowdown unrelated to gene therapy deaths, Novartis CEO says. 2022. Available from: https://www.fiercepharma.com/pharma/novartis-ceo-pins-zolgensma-decline-market-expansion-slowdown-unrelated-death-reports.
42. Trotta F, Guerrizio MA, Di Filippo A, Cangini A. Financial outcomes of managed entry agreements for pharmaceuticals in Italy. JAMA Health Forum. 2023;4(12):e234611.
43. Grubert N, MORSE. Pharmaceutical managed entry agreements. Morse Consulting; 2018.
44. Grubert N. Innovative access arrangements and managed entry. 2023.
45. CSL Behring. Innovative gene therapy available in Germany [press release]. 2023.
46. Philippidis A. Gene therapy briefs: activist investor reported to take $1B stake in BioMarin. 2023. Available from: https://www.genengnews.com/topics/genome-editing/gene-therapy-briefs-activist-investor-reported-to-take-1b-stake-in-biomarin/.
47. BioMarin reports record financial results for the fourth quarter and full-year 2023 and provides financial guidance for 2024 [press release]. 2024.
48. European Medicines Agency. EU/3/18/2015 - orphan designation for treatment of haemophilia A. 2015. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu-3-18-2015.
49. Handschuh T, Horlacher-Hecht M-L, Hohn A. KPMG. Cell and gene therapy challenge. 2022.
50. Sarepta Therapeutics. Accelerating. Available from: https://investorrelations.sarepta.com/static-files/a5db37aa-2cfe-46fb-89ce-47d3ae56adaf.
51. Cardinal Glennon Children's Hospital. Ornithine transcarbamylase (OTC) deficiency. 2024. Available from: https://www.ssmhealth.com/cardinal-glennon/services/pediatric-transplant/pediatric-liver-transplant/ornithine-transcarbamylase-deficiency.
52. Ultragenyx. DTX301 (avalotcagene ontaparvovec): Gene therapy for the potential treatment of ornithine transcarbamylase (OTC) deficiency. 2024. Available from: https://www.ultragenyx.com/our-research/pipeline/dtx301-for-otc/.
53. Moscoso CG, Steer CJ. The evolution of gene therapy in the treatment of metabolic liver diseases. Genes (Basel). 2020;11(8):915.
54. Alliance for regenerative medicines. Cell and gene therapy industry update 2025.
55. BlueRock Therapeutics advances investigational cell therapy bemdaneprocel for treating Parkinson's disease to registrational phase III clinical trial [press release]. 2025.
56. Beitelshees M, Hill A, Rostami P, Jones CH, Pfeifer BA. Pressing diseases that represent promising targets for gene therapy. Discov Med. 2017;24(134):313-22.
57. Conroy G. How gene therapy is emerging from its 'dark age' after years of setbacks, the field is starting to deliver on its promises. Nature. 2022;612(7940):S24-6.
58. Ultragenyx submits biologics license application to the U.S. FDA for UX111 AAV gene therapy for the treatment of Sanfilippo syndrome type A (MPS IIIA) [press release]. 2025.
59. Johnson V. UX111 Reduces heparin sulfate, correlating with benefit in cognitive function in pediatric MPSIIIA. 2024. Available from: https://www.cgtlive.com/view/ux111-reduces-heparin-sulfate-correlating-cognitive-function-pediatric-mpsiiia.
60. Lavery C, Hendriksz CJ, Jones SA. Mortality in patients with Sanfilippo syndrome. Orphanet J Rare Dis. 2017;12(1):168.
61. Kansteiner F. Roche mothballs another hemophilia A gene therapy under Spark amid plans to debut new hematologic asset. 2024. Available from: https://www.fiercebiotech.com/biotech/roche-mothballs-another-hemophilia-gene-therapy-under-spark-it-plans-debut-new-hematologic.
62. Singh P. Sangamo shares plunge after Pfizer ends hemophilia A gene therapy deal. 2024. Available from: https://www.reuters.com/business/healthcare-pharmaceuticals/sangamo-reclaim-hemophilia-therapy-rights-post-pfizer-termination-2024-12-30/.
63. Pfizer. U.S. FDA approves Pfizer's HYMPAVZI™ (marstacimab-hncq) for the treatment of adults and adolescents with hemophilia A or B without inhibitors [press release]. 2024.
64. Hobbs SD, Tripathy K, Pierce K. Wet age-related macular degeneration (AMD). StatPearls [Internet]. 2024.
65. Regenxbio. ABBV-RGX-314 for retinal diseases. Available from: https://www.regenxbio.com/therapeutic-programs/rgx-314/.
66. Blasiak J, Pawlowska E, Ciupińska J, Derwich M, Szczepanska J, Kaarniranta K. A new generation of gene therapies as the future of wet AMD treatment. Int J Mol Sci. 2024;25(4):2386.

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CONTACT

enquiries@cogentia.co.uk
cogentia.co.uk

Cogentia
22 Station Road
Cambridge
CB1 2JD