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# By Any Genes Necessary

## Reflections on a Decade of Gene Therapy, and Key Considerations around Sustainability as we Look to the Future

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>
> **CVS Health**

With the FDA predicting 10-20 cell and gene therapy approvals per year by 2025, we are undoubtedly witnessing an exciting time for personalised medicine. Despite the challenges faced commercially by some of the first gene therapies including Glybera and Strimvelis, Zolgensma has demonstrated early signs of the commercial viability of high-cost, one-time treatments. However, a sobering report from CVS Health estimated that the cost of 11 near-term projects in gene therapy – should they reach the market – would fall anywhere between $14.85 billion and $45 billion in their first 5 years on the market, depending on price and market share. This raises an important question of sustainability. "Curative treatments for such genetic disorders were unfathomable a decade ago; unfortunately, so are the costs of the cures currently in development", as CVS Health put it.

With a raft of gene therapies expected in the coming years, payers may prioritise certain disease areas or simply find that these new innovations are unaffordable when the post-pandemic budget squeeze is considered. If the funding is not there, or the innovations unaffordable, it raises the question of whether the current business model is sustainable and current investments justified. Can everyone be a potential winner, or is it important to take a step back and consider what is needed to make this new approach sustainable? Cogentia propose that a number of factors are likely to contribute to the commercial viability of target disease areas. These include disease burden, prevalence, resource use, current treatment options, cost of comparators, and age at administration. In this paper we seek to explore questions around sustainability for both industry and payers, and by analysing the gene therapy pipeline, we develop a framework that enables us to explore commercial attractiveness of some of the disease areas being targeted, as well as likely obstacles that will be faced by gene therapy manufacturers should they reach the market. For the purpose of this white paper, we are focusing on gene therapy specifically, and so will not be exploring CAR-T or other cell therapy approaches.

# INTRODUCTION

June 26th 2000 was heralded as the dawn of an era of personalised medicine and curative gene therapies (1). However, more than 20 years on from the completion of the first draft of the human genome, the idea of altering a gene to address the root cause of a disease with a single curative dose still feels fairly new (2). The tragic death of Jesse Gelsinger in 1999, an 18-year-old with partial ornithine transcarbamylase deficiency who died from multiple organ failure four days after receiving an experimental gene therapy, as well as the development of leukaemia in multiple patients participating in X-linked severe combined immunodeficiency (SCID) gene therapy trials in the early 2000s, resulted in a slower and more cautious approach to development than was initially anticipated (3,4) (Figure 1). In fact, the first approval of a gene therapy was not until 2012 in Europe and 2018 in the US, with Glybera and Luxturna, respectively, achieving that landmark.

There are signs that the rate of gene therapy approvals is set to accelerate, and in fact the FDA predicts that by 2025 they will be approving 10-20 cell and gene therapies a year, with them consequently hiring an additional 50 clinical trial reviewers in preparation (5,6).

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This owes to a significant boom in pipeline activity (Figure 1) which is driven by multiple factors including:

- Improved safety with the development of adenoviral associated vectors (AAV) and lentiviral vectors
- Greater investor confidence in the commercial potential of gene therapy
- Big pharma's investment in-house and in-licensing gene therapy assets.

As a result, there are now a wealth of gene therapies in the pipeline aiming to address the ultra-rare, as well as the more prevalent genetic disorders.

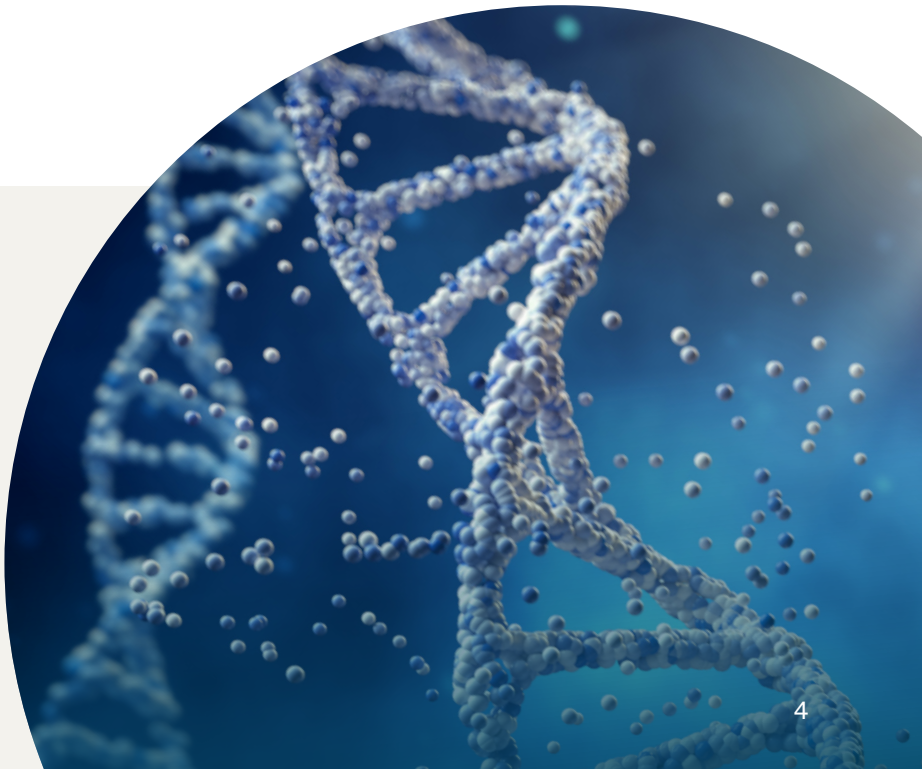
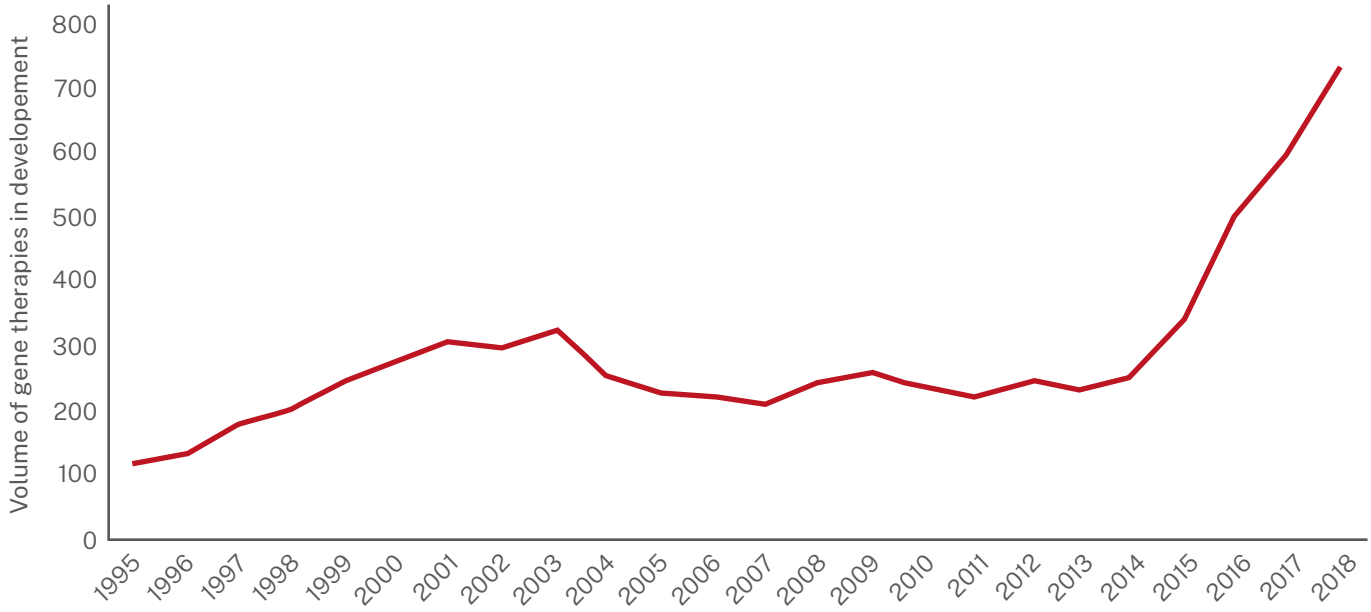


**Figure 1. Gene Therapy Pipeline Volume, Preclinical through Pre-Registration Phase, 1995-2018**




Note: annual volume snapshots are captured in May of each year. Source: (7)

This pipeline boom has resulted in a corresponding boom in interest from both investors and big pharma, driven by the fear of missing out on the next big thing. For instance, the genetic medicines company Sarepta Therapeutics had a market cap of $13 billion prior to the Phase II gene therapy SRP-9001's readout, despite having never demonstrated the efficacy of any of its projects in a placebo-controlled trial at the time (8). Of course, the 50% slashed off Sarepta's market cap by SRP-9001's negative readout in DMD also demonstrates the volatility of the market, as well as the risk companies take in clinical development programmes, particularly in disease areas where successes have been few and far between.

A number of big pharma players have relied on external partnerships and acquisitions in recent years for accelerated entry into the gene therapy space (Table 1).

**Table 1. Select Examples of Recent Gene Therapy Acquisitions**

| COMPANY | ACQUISITION | YEAR | PRICE ($BN) | % PREMIUM* |
|---|---|---|---|---|
| Novartis | AveXis | 2018 | 8.7 | 72 |
| Roche | Spark Therapeutics | 2019 | 4.8 | 122 |
| Astellas | Audentes Therapeutics | 2020 | 3.0 | 110 |
| Bayer | AskBio | 2020 | 2.0** | Private company |
| Eli Lilly | Prevail Therapeutics | 2021 | 1.0 | 80 |

* % premium based on 30-day volume-weighted average stock price. ** $2bn up front, $2bn in milestones.

JPMorgan nicely summarised the factors contributing to this frenzied drive to establish a presence in the gene therapy market: "In our view, the perfect storm is taking shape for investment in gene therapy. Substantial unaddressed need, solid balance sheets of large pharmaceutical companies with excess cash for acquisitions, and maturing pipelines of gene therapy products should support the valuations of smaller gene therapy companies."(9).

However, it is important to consider whether the whole model is sustainable, as ultimately the value of an asset is only realised if the funding is there, and the funding needs to come from either government, companies or individuals. If scientific and clinical advances are making ever more personalised therapies possible, but with high price tags and for an ever-increasing number of patients, can the trend continue?

The pressure on budgets is only likely to increase post-pandemic, and the question is at what point will these potentially curative and yet highly expensive therapies be unaffordable, and therefore not deliver the requisite return on investment for developers? Will manufacturers have to reassess the kind of prices that can be achieved, and could this lead to a tempering of the excitement currently building around gene therapy development, particularly in ultra-orphan diseases?

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## SUSTAINABILITY FOR GENE THERAPY

In order for the surge in the gene therapy pipeline shown in Figure 1 to be sustainable, one must consider what sustainability looks like from a manufacturer perspective, as well as from a healthcare system perspective. Manufacturers must see sufficient returns in order to continue investing (10). Healthcare systems need new gene therapies to be delivered within sustainable budgets, enabling appropriate and timely patient access. The CVS Health white paper on gene therapy put it another way: "curative treatments for such genetic disorders were unfathomable a decade ago; unfortunately, so are the costs of the cures currently in development" (11). Indeed, by calculating 5-year total cost impacts for a selection of near-term assets in the gene therapy pipeline, CVS Health estimated a low market impact of $14.85 billion, and a high market impact of $45 billion (Table 2). Concerningly, this was only based on the 11 projects that are closest to market. It should, however, be noted that half of the market impact is driven by sickle cell disease in CVS Health's calculations, the plausibility of which may be questioned.

**Table 2. CVS Health Estimate of Gene Therapy Near-Term Market Impact**

| Indication | Projected Launch Year | Prevalence + Incidence 2-5 Years | 5-year Total Estimated Cost Impact (2020-2024) $m | |
|---|---|---|---|---|
| | | | Low Market Impact | High Market Impact |
| Haemophilia A | 2020 | 7,360 | 1,460 | 5,830 |
| B-thalassemia major | 2020 | 1,050 | 210 | 550 |
| Sanfilippo syndrome type A | 2021 | 1,150 | 90 | 350 |
| Cerebral adrenoleukodystrophy | 2021 | 6,790 | 670 | 1,790 |
| Adenosine deaminase SCID | 2021 | 1,710 | 130 | 340 |
| Leber's hereditary optic neuropathy | 2021 | 5,480 | 1,090 | 4,340 |
| Choroideremia | 2021 | 4,560 | 900 | 3,610 |
| Haemophilia B | 2021 | 2,620 | 520 | 2,060 |
| Wiskott Aldrich syndrome | 2022 | 3,350 | 500 | 1,340 |
| Metachromatic leukodystrophy | 2022 | 3,420 | 510 | 1,370 |
| Sickle cell anemia | 2022 | 117,020 | 8,670 | 23,400 |

Source: adapted from (11). Low market impact is based on an assumption of a price of $1 million and 30% market share, whilst 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.

## HISTORICAL ANALYSIS

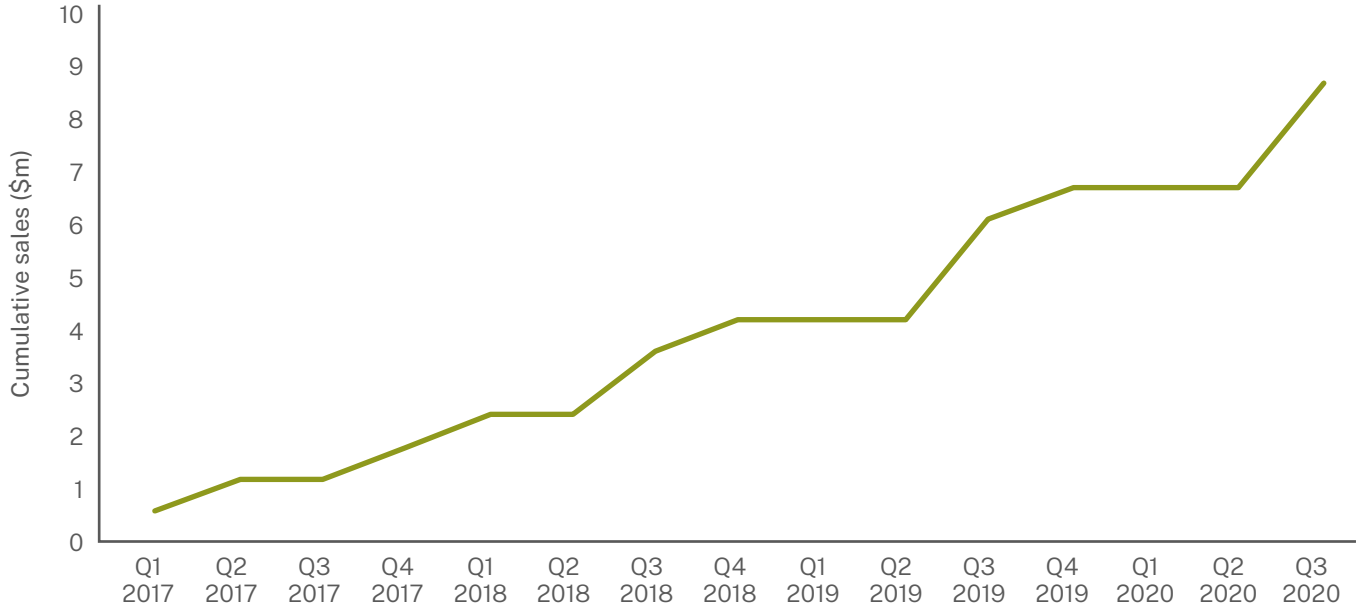
Interestingly, in the context of the booming gene therapy pipeline and M&A activity, the first approved gene therapy in Europe was actually a major commercial flop.

In 2012, uniQure achieved that historic landmark, receiving the first European nod for a gene therapy, paving the way for a new era of personalised medicine. On the 25th October, 2012, Glybera was approved for the treatment of familial lipoprotein lipase deficiency (LPLD), an ultra-rare condition affecting around one in a million people (12). European commercialisation was handled by Chiesi (13). Glybera came with a compelling clinical profile and 100% success rate in patients who received commercial Glybera. One patient in Germany had been hospitalised with LPLD over 40 times prior to receiving Glybera, with not a single admission in the years following treatment (14). Unfortunately, this was reported to be the only patient to receive the drug commercially (15). Whilst a price tag of €1 million was prohibitive back in 2015, another key issue was the ultra-orphan nature of LPLD. Put simply, Chiesi struggled to identify eligible patients. Very small numbers of potential patients combined with the very high cost equated to low demand for Glybera. As a result, the unfortunate fate of the first gene therapy approved in Europe was its withdrawal from the market in October 2017. At the time of withdrawal, uniQure's CEO Matthew Kapusta was quoted as saying "Glybera's usage has been extremely limited, and we do not

envision patient demand increasing materially in the years ahead". But as Kapusta prophetically stated at the withdrawal of Glybera, gene therapy wasn't over, it was "in the very early innings" (16).

The challenge faced by ultra-orphan gene therapies is not unique to Glybera. GSK received EMA approval for Strimvelis in June 2016 for the treatment of a similarly rare disease: adenosine deaminase (ADA)-SCID (17). They priced Strimvelis slightly more conservatively, landing in the region of $650-700k. As a result of the ultra-orphan nature of ADA-SCID as well as the requirement for payers to reimburse treatment at a centre in Italy, Strimvelis typically treats around one patient per quarter (Figure 2). The prevalence is so low that countries such as Germany, Spain, and France negotiate access on a patient-by-patient basis rather than through a centralised health technology assessment. Around two years after EMA approval, Orchard Therapeutics took over the commercialisation, at which time only five patients had been treated with commercial Strimvelis (18).

**Figure 2. Strimvelis Commercial Performance**




Source: Cogentia analysis of Orchard Therapeutics commercial presentations as well as other sources. GSK did not report Strimvelis sales owing to its relatively minor contribution to their overall performance.

There were a number of factors that may have suggested ADA-SCID would be an attractive commercial target for prospective gene therapy companies. It has a high disease burden as a severe immunodeficiency, cost of treatment with haematopoietic stem cell transplantation (HSCT) or alternatives is around €100-€250k, and Strimvelis was the first therapeutic to receive approval in Europe for treatment of ADA-SCID, addressing a clear unmet need (19,20). This is evidenced by the highly positive NICE appraisal. Strimvelis was considered to have a most plausible ICER of <£120,000 per QALY and resulted in a gain of 14.0-19.6 QALYs. It was therefore recommended without the need for a patient access scheme (21).

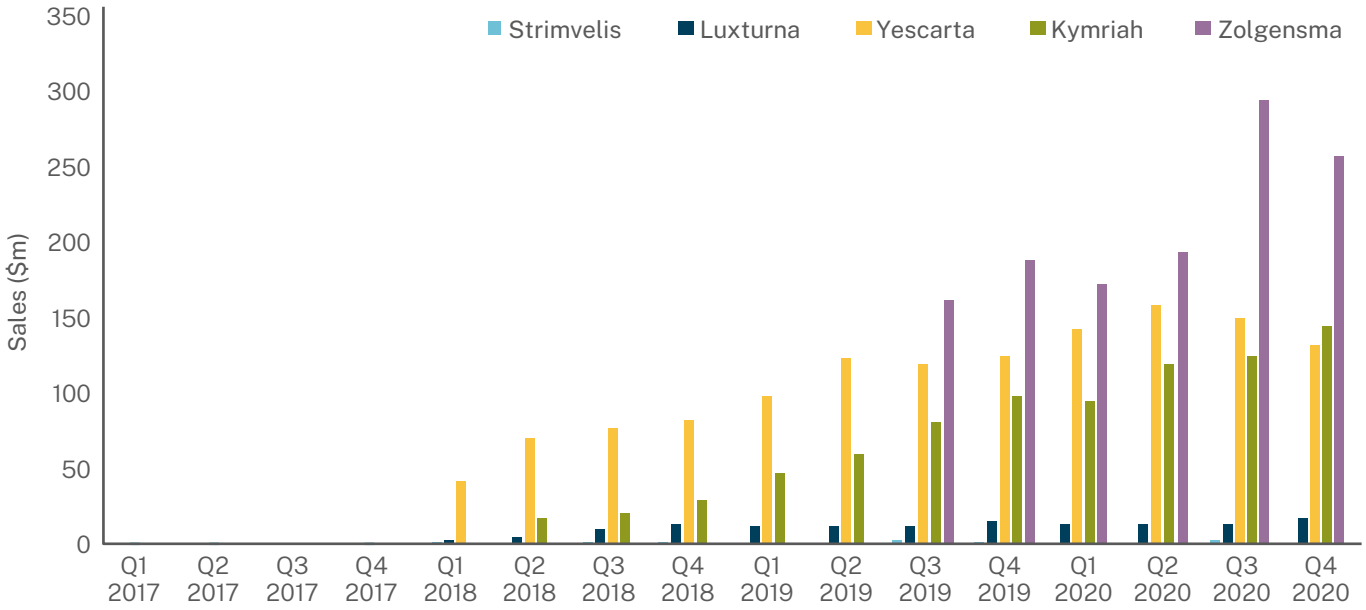
The ultra-orphan nature of ADA-SCID - Orphanet estimate a prevalence of 1-9/1,000,000 in Europe - with corresponding limited patient numbers and budget impact, is certainly favourable from a payer perspective (22). For instance, the NICE 5-year budget impact calculation for Strimvelis was estimated at £2.35 million, or £470,000/year. This is of course less appealing for manufacturers, especially when considering both manufacturing and development costs. This may explain GSK's decision to part ways with Strimvelis, alongside their investigational rare disease gene therapies, handing over the reins to Orchard Therapeutics, as mentioned above.

The challenge of ultra-orphan is illustrated perfectly by the repeat mentions on commercial presentations of manufacturers aiming to move from 'ultra-orphan, to specialist, to prevalent'. Companies such as Orchard Therapeutics have explicitly stated their aim is to accelerate research in 'less rare diseases' (23). This further emphasises the challenge of weighing up risk of failure and cost of development vs NPV of an asset in an ultra-rare condition, where patient numbers are at times prohibitively low.

The case studies of Glybera and Strimvelis may leave the reader questioning the viability of gene therapies from a commercial perspective. They may also raise the question of what big pharma have seen to convince them that gene therapy is the place to invest their sizeable war chests. Whilst the answer is multi-faceted, it can also be summarised in one word: Zolgensma. Zolgensma is starting to realise the potential that has driven growth in the gene therapy pipeline and commitment from big pharma in recent years. Relative to other gene therapies and expensive one-time cell therapies, Zolgensma has flown out of the traps, tracking at blockbuster levels less than 2 years into launch and vindicating the $8.7 billion Novartis stumped up to acquire AveXis (Figure 3).

Whilst the answer is multi-faceted, it can also be summarised in one word: Zolgensma.

**Figure 3. Commercial Performance of Costly One-Time Therapies**




Source: Cogentia analysis of relevant companies' commercial presentations. Roche/Novartis do not report Luxturna sales due to relatively low contribution to overall revenue and so an assumed growth rate has been applied based on Spark Tx reporting up to Q3 2019, assumed constant at 20% year over year. GSK did not report Strimvelis sales owing to its relatively minor contribution to their overall performance, so other sources publicly available sources were used.

Almost immediately after FDA approval in May 2019, Zolgensma settled into treating a steady state of around 100 spinal muscular atrophy (SMA) patients per quarter in the US. The EMA approval in May 2020 contributed further growth to the sales line and demonstrated the importance of ex-US markets for gene therapies (Figure 4). Novartis "Day One" access programme encouraged early uptake following EMA approval, including through schemes such as ATU (France), EAMS (UK), and free-pricing in Germany.

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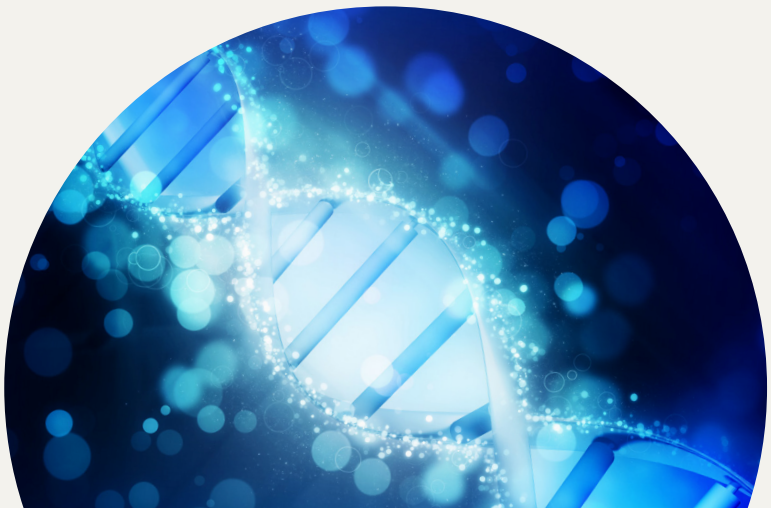
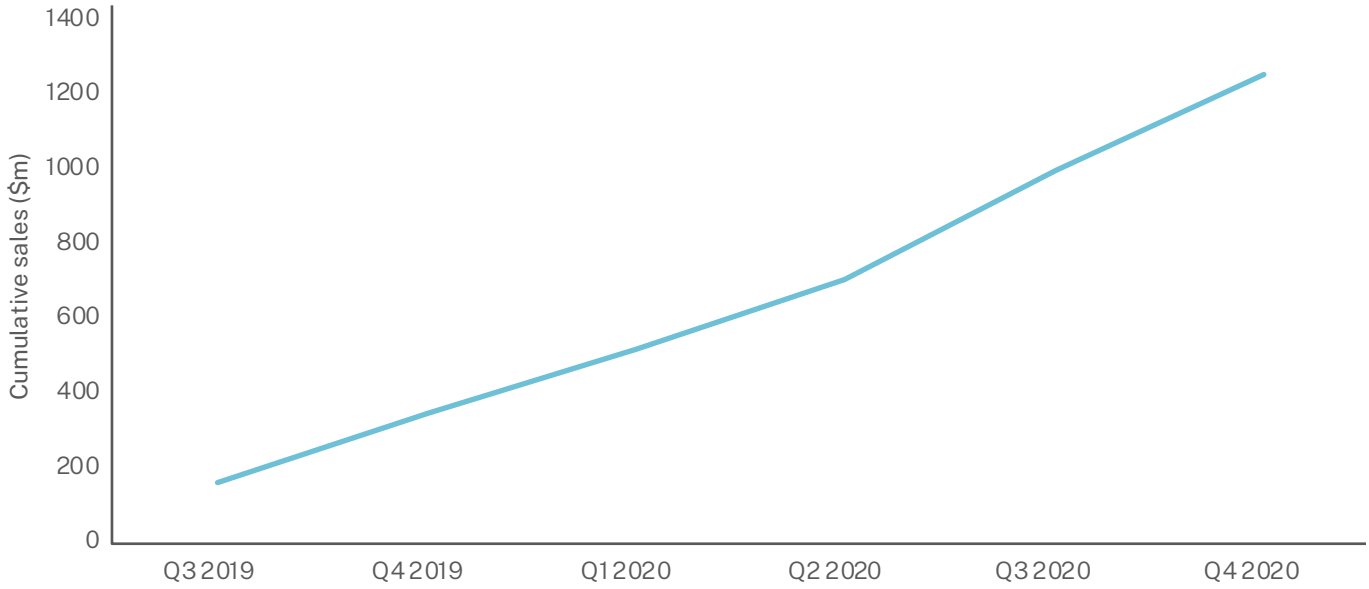


**Figure 4. Zolgensma Commercial Performance**




Source: Novartis commercial presentations.

In Q3 2020, Germany contributed around $85 million in Zolgensma sales (24). As a result, Zolgensma exceeded the orphan budget impact in Germany within months and must go through a full benefit assessment. In fact, payers contacted by Cogentia indicated the performance of Zolgensma was so impressive in Germany that the austerity bill scheduled for the end of 2021 may look to address the mechanisms under which it occurred. This rapid uptake has also resulted in Zolgensma becoming the first subject of new evidence generation rules stipulated under GSAV. As of February 4th, 2021, any physician wanting to prescribe Zolgensma in Germany is obliged to take part in data collection through a registry, with Spinraza the comparator (25).

The "Day One" access programme was designed to enable rapid access to Zolgensma upon EMA approval, before national P&R had been concluded. The programme includes a range of managed-entry options:

- Retroactive rebates
- Deferred payments and instalment options to manage initial budget impact
- Outcomes-based rebates that can be backdated to patients treated during the early access period
- Training for healthcare professionals on the administration of the therapy and follow-up care
- Access to a global registry of SMA patients that is linked to national registries.

Managed-entry agreements (MEAs) like this are increasingly seen as an important solution to gene therapies that have a high cost upfront, with the promise of long-term cost-savings or clinical benefits such as survival, not yet proven. MEAs aim to make the high cost of the one-off treatments more palatable for healthcare payers, who might baulk if faced with the entire cost upfront. Most importantly they ensure any uncertainty regarding long-term effects can be addressed whilst facilitating timely access for patients who are often in desperate need of an effective treatment.

There are plenty of detailed reports on MEAs, and the examples outlined in Table 3 are presented to show the range of options available to manufacturers and payers alike. Some countries have a preference for simpler MEAs such as a dose cap or flat discount rather than more complicated outcomes-based contracts. Take for instance the recent NICE approval of Zolgensma. Whilst the "Day One" access scheme and high price might make Zolgensma an obvious candidate for complex outcomes-based MEAs, NICE and Novartis instead settled on a simple flat discount from list price (26). Also, of note is that often a product can use multiple MEA approaches, for instance an annuity-based outcome-based agreement scheme such as that proposed in Germany for the gene therapy Zynteglo.

### Table 3. Managed Entry Agreements

| MEA | EXAMPLE | COMMENTARY |
|---|---|---|
| Pay-for-performance risk share | CAR-T therapies in Germany | ▶ Ensure payment is contingent on a realised clinical benefit |
| Annuity-based payments | Zolgensma in the US | ▶ Spread the cost over multiple years, but no ability to leverage evidence generated post-approval |
| Outcomes-based agreement | Zynteglo in Germany | ▶ Allows manufacturers to retain a high price assuming clinical benefit exists. Helps to generate RWE for both parties |
| Dose cap | Revlimid in the UK | ▶ Simple measure to limit budget impact |
| Free initial doses | Spinraza in Italy | ▶ Useful for drugs that require a loading dose that results in a higher first year cost |
| Portfolio element | Vertex in the UK | ▶ Allows rapid access to multiple therapies, uncommon approach |
| Confidential discount | Common in most countries | ▶ Manufacturers can maintain a high list price, simple and easily transactable MEA often preferred by payers |
| Price-volume agreement | Particularly common in France | ▶ Helps to control budget impact by ensuring trade-off between price and volume |
| 'Netflix' subscription model | Antibiotics in the UK | ▶ Payment can be based on the value provided by a treatment rather than how much is used |

Examples are illustrative of managed entry agreement options available to manufacturers and include examples from gene therapies as well as other treatment modalities.

The 2nd most expensive treatment to date after Zolgensma is Zynteglo, an ex-vivo gene therapy for transfusion dependent ß-thalassemia (TDT). Zynteglo provides a good example of an outcomes-based agreement. bluebird bio were hailed in some quarters for their innovative approach to MEAs, deferring payment of 80% of the €1.575 million list price of Zynteglo with their first agreement in Germany. bluebird's proposed model was limited to five payments made in equal instalments. An initial payment would have been made at the time of Zynteglo treatment, with four additional annual payments only made if the patient remains transfusion independent (27). However, the recent withdrawal of Zynteglo from the German market after a dispute over price illustrates the point that managed entry agreements are not going to solve all of the problems that come with high cost, one-time therapies. As Professor Richard Barker, OBE, former Director General of the ABPI and current CEO of New Medicine Partners put it in an interview with Cogentia for this piece, "Very expensive, one-time cures by gene therapies pose a novel situation for healthcare payers. It will need almost as much creativity to agree reimbursement models as it does to create the therapies in the lab and clinic".

It is of course worth noting that whilst the prices of Zolgensma ($2.1m) and Zynteglo (€1.575m) may seem astronomical at first glance, they should be viewed in context. For instance, take the example of Cinryze for the treatment of hereditary angioedema. This is the drug that the Institute for Clinical and Economic Review famously slapped with a rather damning cost per QALY gained of $5.9 million, requiring an eyewatering discount of between 97.5% and 99.2% to satisfy the generally accepted cost-effectiveness range of $50,000-$150,000 per QALY. The institute calculated the average lifetime cost of Cinryze at approximately $14.4 million (28). Relative to this, the price of one-time treatment with Zolgensma and Zynteglo does not look quite so exorbitant, assuming they are effective long-term. However, there is the caveat that non-responders to Cinryze can be identified and discontinue treatment at any time, unlike with single administration gene therapies.

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> **Professor Richard Barker OBE, CEO, New Medicines Partners**

## FUTURE CONSIDERATIONS FOR MANUFACTURERS

With a multi-million-dollar price precedent established, coupled with the impressive commercial performance of Zolgensma, the stage appears well set for gene therapy to fulfil its commercial potential. However, the case studies of Glybera and Strimvelis discussed in this paper provide food for thought. How can manufacturers ensure they are targeting the most commercially viable disease areas, and thereby ensure their innovative and potentially curative therapies reach the patients who will benefit from them the most?

So, what predicts commercial performance of a gene therapy, or in fact can we predict this? As discussed earlier, Zolgensma is already tracking at blockbuster status two years into launch, but what factors underpin this success? While the answer is complex and certainly has clinical elements, there are a number of reasons from a commercial perspective that SMA type I was an appropriate target for gene therapy. Firstly, with an incidence of around 1/10,000, SMA is one of the more common rare diseases (29). Zolgensma is infused early on in life with benefits expected to accrue over a lifetime. The disease burden of SMA is particularly significant in type I disease, which can be fatal within 2 years. In fact, SMA is the most common genetic killer of infants and toddlers (30). Hospital visits, rehabilitation, 24/7 care and other resource use put the cost of treating SMA type I at $100-$200k before you even consider therapeutics (31). Lastly, on the point of therapeutics, Spinraza at $750k in year 1 and $375k per year thereafter had already set a precedent for premium pricing, one that Novartis regularly cite when challenged on Zolgensma's price (32).

To summarise, the following made SMA a commercially attractive disease area to target, and have contributed to Zolgensma tracking at blockbuster status soon into launch:

- SMA is a relatively common rare disease
- SMA poses a significant disease burden as the leading genetic killer of infants and toddlers
- A price precedent was set by Biogen with Spinraza, allowing Novartis to price Zolgensma at a high price
- Infusion of Zolgensma is in the early years of life, with benefits expected to accrue over a lifetime.

Another important factor that we will not explore in such detail is patient advocacy. In these often poorly understood diseases where lack of treatment options can be an accepted reality, it is crucial that patient advocacy groups are involved in the design of clinical trials. These groups can support enrolment and ensure the appropriate endpoints are captured. Initiatives like Project HERCULES in Duchenne muscular dystrophy (DMD) are of critical importance in supporting the early adoption of gene therapies, as well as encouraging collaboration between manufacturers to build a better evidence base in support of reimbursement.

Assuming the scientific rationale is there, by applying the factors discussed earlier on - namely disease prevalence, age of infusion, disease burden, cost of treatment, current treatment options, and high price precedent - to a selection of disease areas being targeted by manufacturers, can we predict which disease areas are the most commercially appealing, and which run the risk of suffering a similar fate to Glybera and Strimvelis?

# GENE THERAPY PIPELINE AND DISEASE AREAS TARGETED

Analysis of the gene therapies currently in clinical trials reveals the depth and breadth of the pipeline, from a raft of ultra-rare diseases such as GM1 gangliosidosis and Sanfilippo syndrome type A to much more prevalent conditions including Parkinson's disease and wet AMD (Table 4).

## Table 4. Gene Therapy Assets Currently at Phase I - III

| IND | COMPANY | TARGET DISEASE | CURRENT STATUS |
|---|---|---|---|
| | | | PHASE I/II / PHASE III |
| Cardiology | | | |
| INXN-4001 | Precigen Triple-Gene | Heart failure | |
| RT-100 | Renova Therapeutics | Congestive heart failure | |
| SRD-001 | Sardocor Corp | HFrEF | |
| Dermatology | | | |
| B-VEC | Krystal Biotech | Dystrophic epidermolysis bullosa | |
| KB-105 | Krystal Biotech | Congenital Ichthyosis | |
| Endocrinology | | | |
| BBP-631 | Bridgebio | Congenital adrenal hyperplasia | |
| Haematology | | | |
| AMT-061 | UniQure/CSL | Haemophilia B | |
| BAY 2599023 | Bayer | Haemophilia A | |
| BMN-270 | BioMarin | Haemophilia A | |
| FLT180a | Freeline | Haemophilia B | |
| OTL-300 | Orchard Therapeutics | Transfusion-dependent beta-thalassemia | |
| PF-06838435 | Pfizer | Haemophilia B | |
| PF-07055480 | Pfizer/ Sangamo | Haemophilia A | |
| RP-L102 | Rocket Pharmaceuticals | Fanconi Anaemia Subtype A | |
| SPK-8011 | Spark Therapeutics | Haemophilia A | |
| SPK-8016 | Spark Therapeutics | Haemophilia A | |
| Immunology | | | |
| AAV-AQP1 | MeiraGTx | Xerostomia | |
| MB-107 | MustangBio | X-linked SCID | |
| MB-207 | MustangBio | X-linked SCID | |
| OTL-101 | Orchard Therapeutics | ADA-SCID | |
| OTL-103 | Orchard Therapeutics | Wiskott Aldrich syndrome | |
| RP-L201 | Rocket Pharmaceuticals | Leukocyte adhesion defect – type I | |
| Metabolic | | | |
| 4D-310 | 4D Molecular | Fabry Disease | |
| ABO-101 | Abeona Therapeutics | Sanfilippo syndrome type B | |
| ABO-102 | Abeona Therapeutics | Sanfilippo syndrome type A | |
| ACT-101 | AskBio | Pompe Disease | |
| AT845 | Astellas | Pompe Disease | |
| AVR-RD-01 | AVROBIO | Fabry disease | |
| AVR-RD-02 | AVROBIO | Type 1 Gaucher disease | |
| AVR-RD-04 | AVROBIO | Cystinosis | |
| AXO-AAV-GM1 | Sio Gene Therapies | GM1 gangliosidosis | |

| IND | COMPANY | TARGET DISEASE | CURRENT STATUS |
|---|---|---|---|
| | | | PHASE I/II / PHASE III |
| Metabolic | | | |
| AXO-AAV-GM2 | Sio Gene Therapies | GM2 Gangliosidosis | |
| BMN 307 | BioMarin | Phenylketonuria | |
| DTX301 | Ultragenyx | Ornithine transcarbamylase deficiency | |
| DTX401 | Ultragenyx | Glycogen storage disease | |
| FLT190 | Freeline | Fabry disease | |
| HMI-102 | Homology Medicines | Phenylketonuria | |
| Lenti-D | bluebird bio | Cerebral adrenoleukodystrophy | |
| LYS-GM101 | Lysogene | GM1 gangliosidosis | |
| LYS-SAF302 | Lysogene | Sanfilippo syndrome type A | |
| OTL-203 | Orchard Therapeutics | Mucopolysaccharidosis type I | |
| PBGM01 | Passage Bio | GM1 gangliosidosis | |
| RGX-111 | RegenXBio | Mucopolysaccharidosis type I | |
| RGX-121 | RegenXBio | Mucopolysaccharidosis type II | |
| RP-A501 | Rocket Pharmaceuticals | Danon disease | |
| RP-L301 | Rocket Pharmaceuticals | Pyruvate Kinase Deficiency | |
| SPK-3006 | Spark Tx | Pompe Disease | |
| ST-920 | Sangamo Therapeutics | Fabry Disease | |
| TSHA-101 | Taysha Gene Tx | GM2 Gangliosidosis | |
| VTX-801 | Vivet Therapeutics | Wilson Disease | |
| Musculoskeletal | | | |
| AT132 | Astellas | X-linked myotubular myopathy | |
| FX201 | Flexion Therapeutics | Osteoarthritis | |
| MYO-102 | Sarepta Therapeutics | Limb-Girdle Muscular dystrophy | |
| MYO-201 | Sarepta Therapeutics | Duchenne muscular dystrophy | |
| PF-06939926 | Pfizer | Duchenne muscular dystrophy | |
| RP-L401 | Rocket Pharmaceuticals | Osteopetrosis | |
| SGT-001 | Solid Biosciences | Duchenne muscular dystrophy | |
| SRP-9001 | Sarepta Therapeutics | Duchenne muscular dystrophy | |
| SRP-9003 | Sarepta Therapeutics | Limb-girdle muscular dystrophy | |
| Neurology | | | |
| AAV-GAD | MeiraGTx | Parkinson's disease | |
| AAV-GDNF | AskBio | Parkinson's disease | |
| AMT-130 | uniQure | Huntington's Disease | |
| AT-GTX-501 | Amicus Therapeutics | vLINCL6 disease | |
| AT-GTX-502 | Amicus Therapeutics | Batten disease | |
| AVXS-201 | Novartis | Rett syndrome | |
| AXO-Lenti-PD | Sio Gene Therapies | Parkinson's disease | |
| FBX-101 | Forge Biologics | Krabbe Disease | |
| LX1001 | Lexeo Therapeutics | APOE4-associated Alzheimer's | |
| LX1004 | Lexeo Therapeutics | CLN2 Batten Disease | |
| PBFT02 | Passage Bio | Dementia | |
| PBKR03 | Passage Bio | Krabbe Disease | |
| PR001 | Prevail Therapeutics | Parkinson's Disease | |
| PR006 | Prevail Therapeutics | Dementia | |
| PTC-AADC | PTC Therapeutics | L-amino acid decarboxylase deficiency | |

| IND | COMPANY | TARGET DISEASE | CURRENT STATUS | |
|---|---|---|---|---|
| | | | PHASE I/II | PHASE III |
| Neurology | | | | |
| TSHA-118 | Taysha Gene Tx | CLN1 Disease | | |
| TSHA-120 | Taysha Gene Tx | Giant Axonal Neuropathy | | |
| Ophthalmology | | | | |
| 4D-110 | 4D Molecular | Choroideremia | | |
| 4D-125 | 4D Molecular | X-linked retinitis pigmentosa | | |
| AAV-CNGA3 | MeiraGTx | Achromatopsia | | |
| AAV-CNGB3 | MeiraGTx | Achromatopsia | | |
| AAV-RPE65 | MeiraGTx | Retinal dystrophy | | |
| AAV-RPGR | MeiraGTx | X-linked retinitis pigmentosa | | |
| ACHM-CNGB3 | Applied Genetic Tech | Achromatopsia | | |
| ADVM-022 | Adverum Biotech | Wet AMD | | |
| AGTC 402 | Applied Genetic Tech | Achromatopsia | | |
| AGTC 501 | Applied Genetic Tech | X-linked retinitis pigmentosa | | |
| BIIB-111 | Biogen | Choroideremia | | |
| BIIB-112 | Biogen | X-linked retinitis pigmentosa | | |
| BS01 | Bionic Sight | Retinitis pigmentosa | | |
| CPK850 | Novartis | Retinitis pigmentosa | | |
| GS010 | GenSight Biologics | Leber hereditary optic neuropathy | | |
| GS030 | GenSight Biologics | Retinitis pigmentosa | | |
| GT005 | Gyroscope Tx | Dry AMD | | |
| HMR59 | Janssen | Dry/wet AMD | | |
| rAAV2TYF-CB-hRS1 | TeamedOn | X-linked retinoschisis | | |
| RGX-314 | RegenXBio | Wet AMD | | |
| RST-001 | Allergan | Retinitis Pigmentosa | | |
| SPK-7011 | Spark Therapeutics | Choroideremia | | |

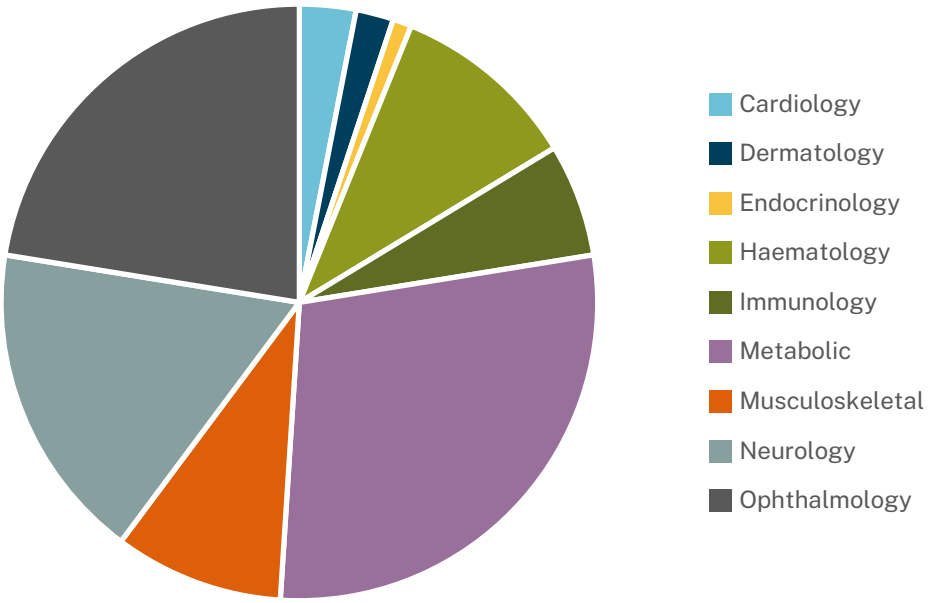
Source: ClinicalTrials.gov. List may not be exhaustive.

Metabolic disorders appear to be the primary target for manufacturers (Figure 5). In particular, the lysosomal storage disorders are a key area of interest. Ophthalmological disorders and neurological disorders are the other most common areas of interest for manufacturers.

There are several disease areas with multiple manufacturers in the clinic, including Parkinson's disease, retinitis pigmentosa, haemophilia (A and B) and MPS type I. This brings to mind another important attribute that is unique to gene therapy, the one-and-done approach. For instance, in haemophilia A let us assume BMN-270 is first to market. Each patient dosed with BMN-270 is then removed from the eligible pool for PF-07055480, SPK-8011, SPK-8016, and BAY 2599023. In ultra-rare conditions, being first to market is therefore critical commercially in terms of treating the prevalent population. Alternatively, if a gene therapy is likely to be second or third to market but there is consensus that it offers better efficacy and/or safety, it is possible that physicians may look to 'warehouse' eligible patients and wait for the better treatment to reach the market. This is of course more likely in a disease where urgency to treat is lower and waiting an additional 6 months is not a case of life and death - think wet AMD rather than SMA type I.

**Figure 5. Therapy Areas Being Targeted in Gene Therapy Clinical Trials**




Analysis based on list provided in Table 4.

Metabolic disorders appear to be the primary target for manufacturers. In particular, the lysosomal storage disorders are a key area of interest. Ophthalmological disorders and neurological disorders are the other most common areas of interest for manufacturers.

## ASSESSMENT OF TARGET DISEASE AREAS AND COMMERCIAL PROSPECTS

After analysing the gene therapy pipeline, we can return to the question posed earlier: is it possible to predict the commercial viability of some of the disease areas being targeted, as well as likely obstacles that will be faced should they reach the market? For the sake of brevity, we will choose 10 diseases to assess, and in doing so aim to predict elements that may prove to be supportive or challenging in the pursuit of the next gene therapies to join Zolgensma in blockbuster status.

As mentioned earlier, a number of disease areas are being targeted by multiple companies with a project at Phase I-III. Several of these will be included for analysis on that basis, alongside an intentionally diverse selection of other disease areas featured in Table 4.

**The 10 disease areas to be assessed:**

1. Parkinson's disease
2. Wet AMD
3. Duchenne muscular dystrophy
4. Haemophilia A
5. MPS type I
6. Fabry disease
7. Cerebral adrenoleukodystrophy
8. Sickle Cell Disease
9. SMA type I
10. GM1 gangliosidosis

**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 5 figures. A prevalence of around 1/10,000 appears optimal (SMA type I allows Zolgensma to command a high price whilst 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 (for example MPS or SMA type I)
- **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 (think Zolgensma and Spinraza).

Taking these factors into consideration, Cogentia has devised a subjective 'commercial attractiveness' matrix and applied it to the 10 disease areas listed above (Table 4). Each parameter is rated on a scale of commercially attractive ( dark green) to commercially challenging ( orange) for gene therapy manufacturers.
For instance, a high price precedent having been set by comparators is a big positive from a commercial perspective ( dark green), whereas cheap alternative options are likely to be a major challenge ( orange).

## Table 5. Comparison of Gene Therapy-Targeted Disease Areas Based on Cogentia's Commercial Predictors of Success Matrix

| DISEASE AREA | PREVALENCE | AGE IN CLINICAL TRIALS (YEARS) | DISEASE BURDEN | DIRECT TREATMENT COSTS | CURRENT TREATMENT OPTIONS | COST OF COMPARATOR/ YEAR* | HIGH PRICE PRECEDENT Y/N |
|---|---|---|---|---|---|---|---|
| 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 | $50-100k (one off) | N |
| Wet AMD | ~3 million worldwide | 50+ | Most people move from diagnosis to legal blindness in 10 years without treatment | $10-20k per year, including diagnostic and assistance with daily activities | Lucentis, Eylea | $20-40k | N |
| Duchenne Muscular Dystrophy | 5/100,000 | 4-7 | Rapidly progressive, lethal neuromuscular disorder. Common to be wheelchair-bound by age 8-14. Life expectancy <30 years | Ranging from $10k-80k per year as disease progresses | Corticosteroids, Viltepso, Exondys 51, Vyondys 53 | $300k-$1m | Y |
| Haemophilia A | 5/100,000 | 18+ | Life expectancy around normal with extensive treatments | BioMarin put the cost of lifetime treatment of haemophilia A at $25m | Factor VIII, Hemlibra | $400-$700k | Y |
| MPS Type I | 1/100,000 | 4 months+ | Significant developmental delay + cognitive decline. Life expectancy <10 years | Poorly documented, likely to be well over $100k per year in severe disease | Aldurazyme/HSCT | $200-500k | Y |
| 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 | $200-400k | Y |
| Cerebral Adreno-leukodystrophy | 2/100,000 | >17 years | Progressive neurological symptoms with rapid loss of function. Life expectancy in childhood CALD 5-10 years post-diagnosis | Poorly documented. Estimated at >$100k/year driven by 24/7 care | HSCT | $150-200k (one off) | N |
| Sickle Cell Disease | 30/100,000 | 12-35 | Sickle cell crises, infections, anaemia with vaso-occlusive crises. Life expectancy 45-50 years | ~$60k per year, higher depending on number of VOC | Adakveo, Oxbryta | $100-150k | Somewhat |
| SMA Type I | 10/100,000 | <6 months | Type 1 is typically fatal within 2 years, and involves a lack of developmental milestones | $100-200k per year, driven by hospital visits, rehabilitation and other costs | Spinraza, Evrysdi | $350-750k | Y |
| GM1 Gangliosidosis | 0.5/100,000 | 0.5-12 | Type 1 is the most severe, characterised by developmental regression. Life expectancy in type 1 is 2-3 years | Varies based on type. Type 1 has costs ~ $150-200k/year | No approved treatment | – | N |

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. Colour coding spans commercially favourable ( deep green) to commercially unfavourable ( orange). 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 orange 0 points.

## Table 6. A Ranking of Commercial Attractiveness of Gene Therapy-Targeted Disease Areas Based on Cogentia's Matrix

| DISEASE AREA | PREVALENCE | AGE IN CLINICAL TRIALS (YEARS) | DISEASE BURDEN | DIRECT TREATMENT COSTS | CURRENT TREATMENT OPTIONS | COST OF COMPARATOR/ YEAR | HIGH PRICE PRECEDENT Y/N | AVERAGE |
|---|---|---|---|---|---|---|---|---|
| DMD | 3 | 3 | 4 | 2 | 4 | 4 | 4 | 3.4 |
| SMA type I | 4 | 4 | 4 | 3 | 1 | 4 | 4 | 3.4 |
| MPS Type I | 1 | 4 | 4 | 3 | 2 | 3 | 4 | 3.0 |
| Haemophilia A | 3 | 1 | 1 | 4 | 1 | 4 | 4 | 2.6 |
| Fabry Disease | 4 | 1 | 2 | 2 | 1 | 3 | 4 | 2.4 |
| Sickle cell disease | 3 | 2 | 3 | 2 | 2 | 2 | 1 | 2.1 |
| GM1 Gangliosidosis | 0 | 3 | 4 | 3 | 4 | 0 | 0 | 2.0 |
| Cerebral ALD | 1 | 3 | 4 | 3 | 3 | 0 | 0 | 2.0 |
| 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 orange 0 points.

By using the matrix displayed in Table 5, 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. For instance, and as discussed earlier, a look at SMA demonstrates why Zolgensma has performed so well. SMA is a relatively common rare disease. Zolgensma is infused early on in life with benefits expected to accrue over a lifetime. Type 1 SMA in particular is extremely severe, with life expectancy typically in the range of 2-3 years prior to the launch of Spinraza. Resource use is high due to a large number of hospital visits and rehabilitation, and current SoC Spinraza costs $750k for the first year alone. As a result, SMA sits joint top of our commercial attractiveness ranking (Table 6).

The other disease areas assessed display a high degree of heterogeneity, scoring a range of 3.4/4 to 0.3/4 on the predictive factors laid out earlier on. It is interesting to note that most of the 10 disease areas have things going in their favour commercially, as well as things that may count against them. For instance, if we select three of the ten disease areas analysed it is easier to see why manufacturers saw some of them as more attractive targets than others, with wet AMD in particular likely to prove challenging, even before the ripples of ADVM-22's recently announced suspected unexpected serious adverse reaction (SUSAR) of hypotony are felt. For a contrasting view, we have selected one disease area that ranks at the top in terms of commercial attractiveness, one in the middle, and one towards the bottom (Table 6).

## DUCHENNE MUSCULAR DYSTROPHY

7th January 2021 marked a significant day for the DMD community, as well as one of contrasting fortunes for manufacturers. As Pfizer announced that the first patient had been dosed with PF-06939926 in their Phase 3 CIFFREO study, Sarepta Therapeutics revealed their own DMD candidate SRP-9001 had failed to beat placebo at Phase II, almost halving Sarepta's share price in the process (33,34). With Evaluate forecasting more than $3 billion in peak annual sales for SRP-9001 at one stage, it is easy to see why investors got cold feet after the Phase II readout.

As shown in Table 5, aside from the clinical, DMD makes a lot of sense commercially. Patients receive the gene therapy at age 4-7, and thereafter potentially accrue a lifetime of benefits. DMD poses a significant burden as a rapidly progressive disease that often leaves patients wheelchair-bound before they reach their teens. Life expectancy typically does not extend beyond the third decade. Current standard of care is corticosteroids, which are of course not disease specific, and typically come with a questionable benefit: risk profile long-term. Therefore, the unmet need for a curative treatment is significant. Whilst corticosteroids are often inexpensive generic medicines, a number of treatments aimed at subsets of the DMD population have entered the market with prices in the range $300k-$1m depending on weight, setting a strong benchmark for prospective gene therapies and as discussed in the following paragraph, setting an incredibly low bar for sufficient evidence packages for approval in the US (35).

Further supporting the need for new treatments is the FDA approval of viltolarsen despite a lack of definitive verification of its efficacy. In the announcement of viltolarsen's approval, the FDA qualified their decision: "in making this decision, the FDA considered the potential risks associated with the drug, the life-threatening and debilitating nature of the disease, and the lack of available therapies" (36). Recall also the approval of Sarepta's Exondys 51 (eteplirsen) in 2016 that sparked controversy with a tense advisory panel and internal dispute that led to a number of staff leaving the agency (37). Data from a very small number of patients had suggested Exondys 51 helped DMD patients produce around 1% of the normal level of dystrophin (38). A damning Institute for Clinical and Economic Review report followed with CMO David Rind pulling no punches "With eteplirsen, we heard about the hopes of parents that the treatment is beneficial. However, the wholly inadequate evidence base from the manufacturer has created such doubt that payers, faced with the outrageously high price charged by the manufacturer, have created extremely narrow coverage policies; no other country has even approved the treatment. We are left where no one can know whether a useful therapy is being administered to a small number of children while others around the world are denied therapy by payer barriers and regulatory approval, or whether the patients receiving eteplirsen are being given a useless, high-priced treatment" (35). Perhaps even more damningly the institute could not even estimate a fair value-based price because the evidence base was considered to be so low.

Finally, – and not included in Table 5 - thanks to the stellar work of project HERCULES, advocacy in DMD is especially strong (39). In summary, if the clinical rationale is there and the CIFFREO readout is positive, PF-06939926 should be an especially attractive asset for Pfizer, particularly in light of SRP-9001 coming up short at Phase II. Of course, it must be added that other factors will contribute to the uptake of PF-06939926, including further understanding of the complement-related serious adverse events that have at times plagued its development (40).

A number of treatments aimed at subsets of the DMD population have entered the market with prices in the range $300k-$1m depending on weight, setting a strong benchmark for prospective gene therapies.

### HAEMOPHILIA A

Both haemophilia A and B are hotly contested battlegrounds for prospective gene therapy players. Pfizer and partners Sangamo are competing with BioMarin's Valrox to be first to market for haemophilia A, although both have been set back by concerns over waning efficacy. In August 2020 the FDA issued BioMarin a complete response letter for that very reason, wiping $7.5 billion off their market cap in the process (41). Whilst Table 5 shows that certain elements – such as prevalence, age of patients in clinical trials, and life expectancy – may suggest haemophilia A could be a challenging target commercially, all of this is offset by one key factor. BioMarin estimated the lifetime cost of treating haemophilia A at $25 million, driven by a cost of $300-$500k per year for factor VIII replacement and a life expectancy close to normal. In this regard, even if a gene therapy were to be priced at $3m as BioMarin posed, it would still offer significant cost-savings were the effect to be sustained over a lifetime. This last point is of course up for debate given the serious question marks over durability of effect hanging over both Pfizer/Sangamo and BioMarin's gene therapies (42).

### PARKINSON'S DISEASE

Along with wet AMD, Parkinson's disease is the obvious outlier in Table 5. A prevalent population of 10 million globally and an average age of onset around 60 years seems an odd target for a gene therapy. With this age of onset, potential benefits from a gene therapy will be realised for 50-60 years less than for those with SMA type I or MPS type I. Pricing of comparators is also not excessive, likely owing to the large addressable pool of patients. Eligibility criteria for the AXO-Lenti-PD trial requires patients to be eligible for surgery, and so a viable comparator may be deep brain stimulation at a one-off cost of around $50-100k for bilateral DBS. While there is a significant unmet need for treatments that delay or even halt disease progression, a gene therapy that requires brain surgery is likely to be reserved for more severe patients in line with clinical trial eligibility, where the disease has already progressed to a stage where quality of life is reduced. Should any of these PD-targeted gene therapies reach the market, it will be fascinating to see what price point manufacturers can justify, and whether the commercial performance can defy our predictions.

## CONCLUSIONS

As we have discussed, it is an exciting time for gene therapy with a whole host of players from big pharma to smaller start-ups anxious not to miss out on the opportunity. The disease areas being targeted are incredibly diverse, from ultra-rare diseases like GM1 gangliosidosis to diseases with a global prevalence in the millions like wet AMD and Parkinson's disease. Whilst the potential of gene therapy is highly attractive commercially, and life-changing clinically, it remains critical for manufacturers and payers to consider the sustainability of the current trend. The CVS market impact calculations in Table 2 paint a stark picture; there is no point in having a raft of potentially curative gene therapies if the healthcare system cannot afford to provide them to the patients who often so desperately need them.

Back in 2017, Bloomberg wrote an excellent article titled 'When the Patient is a Gold Mine: The Trouble With Rare Disease Drugs' centred around the aggressive Alexion sales practices that drove Soliris to around $4 billion annual sales despite an eligible patient population of fewer than 11,000 (43). Were this to repeat itself on a larger scale such as that seen in the gene therapy near-term pipeline, it is highly unlikely that healthcare systems would be able to cope. In contrast, if a gene therapy is truly curative, or likely to save an enormous amount of money downstream such as with the example of haemophilia, a price of $2-3 million should not be baulked at, and may actually be considered good value for money.

Of course, newly developed gene therapies do not have the data to prove efficacy, safety, and cost-effectiveness over any extended period at the time of launch, and thus significant uncertainties remain, uncertainties that can be somewhat addressed through the use of managed-entry agreements. By deferring payment and leaving a meaningful chunk of the value at risk, contingent on achieving pre-agreed clinical outcomes such as sustained reduction/increase in a key biomarker or reduction in need for other treatments, manufacturers are able to obtain an attractive price assuming their drug does what it says on the tin, whilst payers are able to ensure they are getting value for money. This also allows both sides to establish longer-term real-world data that can be used for subsequent negotiations, helping to address uncertainties whilst ensuring timely access for patients.

As we move towards the 10-20 cell and gene therapy approvals predicted per year by 2025 (in the US at least), it is highly likely that managed-entry agreements will increasingly be favoured. However, the example of Zynteglo's withdrawal in Germany illustrates the point that managed-entry agreements are not a silver bullet. Had bluebird and payers in Germany come to an agreement, it would have been interesting to see how the proposed outcomes-based agreement would have worked in practice. If €315,000 was on the table each year for transfusion-independence and a patient was on the brink of requiring a transfusion just days before their treatment anniversary, could bluebird have contested this? This again links rather nicely back to the Bloomberg article on Soliris; these MEAs will have to be entirely unambiguous to avoid a raft of litigation or the potential for overly aggressive sales tactics.

Additionally, as gene therapy moves from rapidly fatal and severely debilitating diseases with no treatment alternatives to those where disease burden is lower and alternatives exist, it is not just commercial execution that manufacturers need to consider. Consideration should also be given to the potential challenge this could pose to clinical trial recruitment. Toxicity scares such as those seen recently with Adverum's ADVM-022 should concern manufacturers who are targeting disease areas that are at least somewhat adequately served by current treatments. Will patients be willing to take the risk of enrolling for a gene therapy trial when there are already reasonably effective treatments on the market? A gene therapy cannot progress through the clinic if patients do not see the benefit outweighing the risk and choose not to enrol. This is particularly true for early adopters, those that are the first to receive these experimental therapies.

In conclusion, whilst the potential of gene therapy is extremely promising both for pharma and for patients, care must be taken to ensure the wave of gene therapies in the pipeline does not end up overwhelming healthcare systems worldwide. Whilst some disease areas such as haemophilia A (for cost offsets), DMD (for disease severity + poor alternative treatments) and SMA (for expensive comparators + disease severity) seem obvious choices for manufacturers from a commercial perspective, it will be fascinating to follow progress in less obvious disease areas such as wet AMD, where there are already relatively effective treatments approved, age of onset is typically 50+ and global prevalence is numbered in the millions rather than the thousands.

### WHAT HAVE WE LEARNED?

It is undoubtedly an exciting time for gene therapy, with Zolgensma demonstrating the commercial viability of expensive, one-time treatment. As companies aim to carve out a piece of the market, it will be important for manufacturers and payers alike to consider the sustainability of the trend. Whilst disease areas like DMD and haemophilia A appear commercially viable, it will be fascinating to follow progress in less obvious disease areas such as wet AMD.

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## ABOUT US

Cogentia was founded in 2010 with our head office located in Cambridge, UK. Since then, our company has worked with a wide range of pharma and biotech clients, recognising the importance of market access support throughout early product development through to in-market support.

We have a proud history of providing original thinking, insightful advice and full alignment with each client's product and project to deliver quality outputs on time.

We offer an integrated team of market access experts – with skills in both technical disciplines such as economic evaluation, health technology assessment, evidence synthesis and also in strategic aspects of market access such as value proposition development, payer research and global value dossiers.

Cogentia teams work in close partnership with our clients - often on long term engagements - ensuring alignment with project requirements, driving clear communication and optimal outcomes.

Cogentia specializes in market access, offering a full range of services including:

- Value Proposition Development
- Pricing research
- Market Access Strategy
- Valuation and Sales Forecasts
- Economic Evaluation
- Evidence Synthesis
- Health Technology Assessment (HTA)
- Stakeholder Engagement

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