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Gene Therapies: Unlocking the opportunity for patient access

After the successful approval and commercialization of the first gene therapy treatments worldwide, reviewing value and access strategy, implementation, and critical capabilities can offer key learnings for the pharmaceutical industry's gene therapy age.

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Key takeaways

To scale access for gene therapy in a rare disease, efforts in five key areas are needed:

- **Use a valuation approach tailored to one-time therapies**, exploring a variety of factors including innovative analogues for long-term transformative impact, comparison of other treatment costs over an extended period, valuation of a statistical life, and the welfare economics theory.
- **Invest early in natural history studies and real world evidence generation** to address payer uncertainties, support label discussion, and expand contracting options.
- **Reframe and expand innovative pricing and contracting models,** proposing outcome-based agreements and installments where needed to alleviate payer challenges.
- **Quickly establish access pathways to address unmet needs**, re-thinking the launch sequence, exploring alternative pathways to enable reimbursement, and facilitating patient access to therapies immediately after regulatory approval.
- **Build strong partnerships to support healthcare systems holistically**, in the development of innovative regulatory, access, contracting, and evidence generation pathways, to ultimately drive access, including in low- and middle-income countries.

For decades, gene therapies have been limited to clinical trials, with the prospect of revolutionizing the treatment of genetic disorders at an impactful scale just out of reach. Only in the past ten years have gene therapies transitioned to market, with regulators approving treatments in therapeutic areas ranging from oncology to rare diseases. Ensuring patient access to these treatments though, has proven difficult. Even after decades of research, development, and investments, early gene therapies have been challenged to ensure patient access in select markets [1, 2].

Despite these challenges, gene therapy research and development continue to grow, expanding by approximately 30% annually on average over the past five years [3]. By the end of June 2023, there were more than 2,000 gene therapies in development, from preclinical research to phase 3 clinical testing, spanning multiple therapeutic areas [3, 4]. With more than 30 gene therapies in phase 3 clinical trials and pre-registration, the number of approvals is expected to continue to rise [3].

Novartis Gene Therapies portfolio includes Zolgensma® (onasemnogene abeparvovec), a one-time gene therapy used to address the genetic root cause of spinal muscular atrophy (SMA).

Zolgensma was approved by the U.S. Food and Drug Administration (FDA) in 2019, the European Medicines Agency in 2020, and other health and regulatory authorities in other countries, and has been used to treat more than 3,500 patients across the globe, including clinical trials, managed access programs, and commercially [5]. The treatment's access worldwide offers insights into how gene therapies can be a sustainable, commercially viable category.

Scaling Access for Gene Therapy in a Rare Disease: Lessons Learned

Historically, large cap pharmaceutical companies mostly developed and marketed small molecules and biologics for acute or chronic disease management. With the absence of key analogues in cell and gene therapies at the time of launch, Novartis Gene Therapies had to rapidly rethink commercial and access models for Zolgensma. Five practices have been instrumental in ensuring patient access (see Exhibit 1), resulting in Health Authority approvals in more than 50 countries and access pathways in more than 35 countries worldwide [6].

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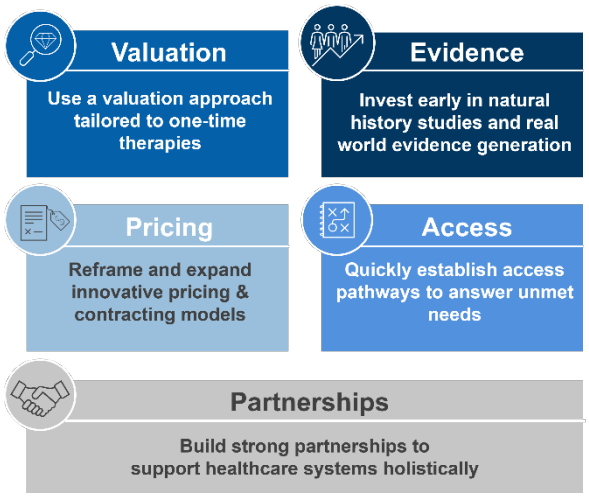
Exhibit 1

Five practices for launching a one-time gene therapy



1. Use a valuation approach tailored to one-time therapies

The current cost effectiveness modeling methodology, used by Health Technology Assessment (HTA) bodies, has been designed with chronic therapies in mind, and assesses the value of medical treatments by integrating both short-term affordability and long-term value for money [7]. A different approach is needed in order to appropriately value a one-time therapy with potential long-term benefits. Exploring a variety of factors, including innovative analogues for lifelong transformative impact (e.g., transplant surgery), comparison of other treatment costs over an extended period of time, valuation of a statistical life with a systematic review and a quantitative analysis, and the welfare economics theory, can help demonstrate the value of one-time treatments. As independent organizations like Institute for Clinical and Economic Review and HTA bodies like the National Institute for Health and Care Excellence will assess an increasing number of therapies, Zolgensma's value assessment framework may serve as a future example for other one-time therapies.

2. Invest early in natural history studies and real world evidence generation

One-time therapies face evidence challenges beyond the typical limitations of rare disease clinical trials. These include demonstrating long-term efficacy and safety within the confines of time-capped, limited endpoint trials, as well as small patient pools, use of surrogate endpoints, and the ethical concerns of placebo-controlled trials. Addressing these uncertainties is imperative to reinforce medical and payer confidence in therapies' long-term efficacy and safety. This is where real world evidence (RWE) can fill data gaps in one-time therapy trials – but to benefit from evidence generation, companies must start investing prior to launch. Investing in natural history studies, developing disease registries where needed (e.g., Novartis' RESTORE registry for patients with SMA [8]), and/or partnering with other patient registries, organizations and health care stakeholders, can improve understanding of the disease, support clinical trial design and label discussions, and uncover patient unmet need and therapies' real world clinical efficacy profile. RWE can also expand contracting options (e.g., outcomes-based contracts with endpoints beyond clinical trials) and support policy and practices in the disease care setting. In some countries, including Germany, health authorities mandate RWE collection for certain therapies [9].

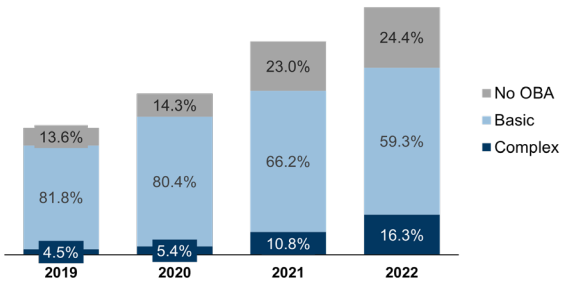
3. Reframe and expand innovative pricing and contracting models

The efficacy, durability, and affordability of one-time therapies are common concerns for health systems and payers — but outcomes-based agreements (OBAs) can help address these uncertainties by tying cost to specific outcomes, and installments can help alleviate budgetary constraints. These innovative contracting models have been preferred by payers in and outside of the US (see Exhibit 2) and have the potential to create new pathways for one-time therapies. For example, the first OBA to be part of Brazil's HTA agency review was Zolgensma's [10], paving the way for future advanced therapies to get access via risk-sharing, pay-over-time arrangements in the country.

Over time, contracting models have become more complex (see Exhibit 2), including differential outcomes by population and new and/or more nuanced endpoints [11]. While such complexity may be warranted in specific cases, it could also place implementation at an increased risk, delaying patient access. Therefore, it is imperative to balance benefits and risks of OBAs cautiously and utilize these contracts when appropriate based on payer and stakeholder needs.

Exhibit 2

Cumulative percentage of complex and basic outcomes-based agreements (OBAs) for Zolgensma from 2019 to 2022 [11]



4. Quickly establish access pathways to address unmet needs

High unmet need for rare diseases can catalyze governments and manufactures alike to co-create rapid access pathways. Three learnings have emerged:

Don't follow the typical launch sequence: Simultaneously work to secure access pathways in traditional markets and other countries with high unmet need. Especially when alternative treatment options are limited, manufacturers should re-think their market prioritization and flatten their launch sequence. Early access agreements can be instrumental in rapidly providing patient access beyond traditional markets. Three years since Zolgensma's FDA approval, countries such as Ecuador and Egypt [12, 13] gained access to the treatment through early access agreements. Thoughtful execution of this approach is critical. As countries become increasingly interconnected, decisions in one country can have global ripple effects beyond traditional International Reference Pricing rules [14].

Prioritize facilitating patient access to therapies immediately after regulatory approval: "Day One" Access agreements, which leverage both well-established routes (e.g., France's Autorisation Temporaire d'Utilisation [15]), and novel programs developed in partnership with local healthcare authorities (e.g., Alberta, Canada [16]) can make therapies available immediately following regulatory approval. The Zolgensma "Day One" Access program was designed to work within existing, local pricing and reimbursement frameworks, and to offer ministries of health and reimbursement bodies a variety of flexible options that could be implemented immediately after regulatory approval to support access before final pricing and reimbursement decisions [17]. Governments may also choose to build on these once novel programs to the benefit of other rare diseases more broadly. For example, in the Netherlands, the Orphan Drug Access Protocol pilot program, launched in 2022, serves to improve access to orphan drugs in the country before the finalization of pricing and reimbursement processes [18].

Don't restrict funding to traditional sources: Explore all alternative pathways to enable reimbursement, such as separate government funds for rare diseases, public/private partnerships or local organizations. Bringing transformative therapies to a country should be a shared responsibility between governments, manufacturers, policy makers, health authorities, and the larger healthcare community. Advancing early-stage dialogue on atypical partnership models may expedite downstream access over time.

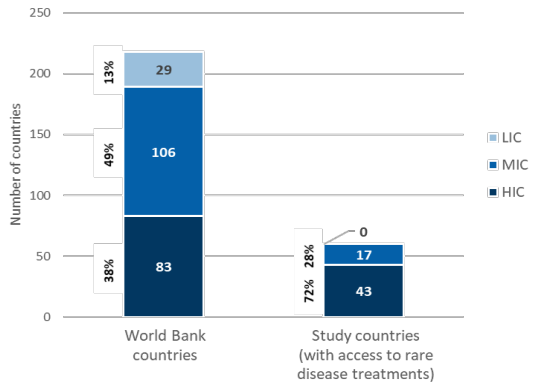
5. Build strong partnerships to support healthcare systems holistically

Bringing a one-time therapy to market requires strong partnerships with key stakeholders in the corresponding ecosystems, such as ministries of health, HTA bodies, policy makers, patient organizations, and more. Proactive and early engagement with partners is needed for the development of innovative regulatory, access, contracting, and evidence generation pathways that support healthcare systems and drive access. For example, Novartis Gene Therapies has been working with the Brazilian government, Sindusfarma, a Brazilian pharmaceutical industry trade association, and other advanced therapy companies to shape new regulations for advanced therapies. By establishing clear regulatory pathways for rare disease treatments with specific biosafety considerations, this partnership is paving the way for broader access to advanced therapies in the country [19].

Rare disease treatments are disproportionally accessible in high-income countries compared to middle- and low-income countries (see Exhibit 3 [20]). Efforts to enhance drug access and availability are paramount across the economic spectrum, as many rare disease treatments are available in only about 50% of high-income countries (see Exhibit 3).

Exhibit 3

Availability of rare disease therapies by country by income with World Bank classification [20]



LIC – Low-income countries; MIC – Middle-income countries; HIC – High-income countries.

Comprehensive partnerships across the healthcare ecosystem go a long way to improve the disease care model, raise disease awareness, and enable patient identification, especially in low- and middle-income countries where healthcare systems strengthening may be needed. These partnerships are designed to build healthcare system capabilities for gene therapies and can support RWE collection, clinical experience development, and institutional and healthcare professional training and development. For example, Novartis Gene Therapies is collaborating with Chile's Ministry of Health to build capabilities in the public health system for the management of SMA and gene therapies, in part by supporting the continuous training of health professionals in public and private health sectors.

How to organize for success

Redefining access and driving uptake for one-time therapies for rare diseases is intrinsically related to reviewing and revamping a global value and access strategy—and this requires a new internal operating model, which will look and feel very different from current biotech and large-pharma set-ups.

Integrate value & access

To be able to address challenges posed by launch, manufacturers may benefit from crafting an integrated Value & Access operating model bringing together Health Economics and Outcomes Research, RWE, Translational Access, and Pricing teams. The complexity of bringing one-time therapies to market requires increased collaboration between all teams to maximize patient access. Creating an integrated Value & Access function ensures a shared vision and collaboration, and improves ease and speed while working with other functions such as Regulatory, Medical, Marketing, Policy, and Patient Advocacy. Such an integrated team is also more likely to challenge the status quo due to the diversity of perspective and expertise each member brings, and to reset, reframe, and establish a new operating model suited to 21st century medicines.

Novartis Gene Therapies followed this model in Zolgensma's launch, which allowed for an efficient and seamless implementation of evidence-to-access strategies, creating bridges for clinical partnership in designing access strategies and building evidence generation and valuation approaches to support sustainable access.

Create an agile team & foster an innovative mindset

Emphasizing innovation within an agile team is fundamental to tackling the high complexity and uncertainty of one-time therapies.

Four key pillars help build and foster a thriving environment:

- *psychological safety,* which allows the team to feel safe taking risks and being vulnerable,
- *focus on improvement*, which allows for a test-and-learn approach and empowers the team to experiment,
- *optimized workflow* between all sub-teams within their functions, which ensures maximum support and diversity of thought, and
- *creativity,* which fosters a problem-solving mindset and nurtures associates' ability to think freely.

In such an environment, experts from a variety of backgrounds can cross-pollinate to develop innovative, compelling, and scalable approaches.

Treat it like a team partnership

A successful one-time therapy requires not only a strong and innovative Value and Access team; it mandates an efficient cross-functional way of working across the broader organization. The solutions needed to reach broad patient access will need input and expertise from teams such as Policy, Patient Advocacy, Medical, Finance & Accounting, Ethics, Risk & Compliance (ERC), Legal, and more. For example, developing and implementing OBAs requires extensive collaboration between the Value & Access, Medical, and Finance & Accounting teams to ensure risks are appropriately assessed and accounted for. Additionally, Early Access Agreements require broad input from ERC and Legal. This cross-functional way of working elevates the discussion by ensuring that access

becomes the entire organization's work, purpose, and existence.

In the pharmaceutical industry's gene therapy age, rethinking early value and access strategy in the context of the five practices (using a tailored valuation approach, investing in RWE early on, expanding innovative pricing and contracting models, quickly establishing access pathways to address unmet needs, and building partnerships in the healthcare systems) and investing in critical capabilities can support rapid scale for world-wide access to one-time therapies. Achieving health authority approval may just be the start: the work of strategic disease valuation versus current standards of care has to be initiated at the pre-clinical stage. Then, converging access, HTA and regulatory schools of thought will determine the success and rapid scale-up of coverage and reimbursement.

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