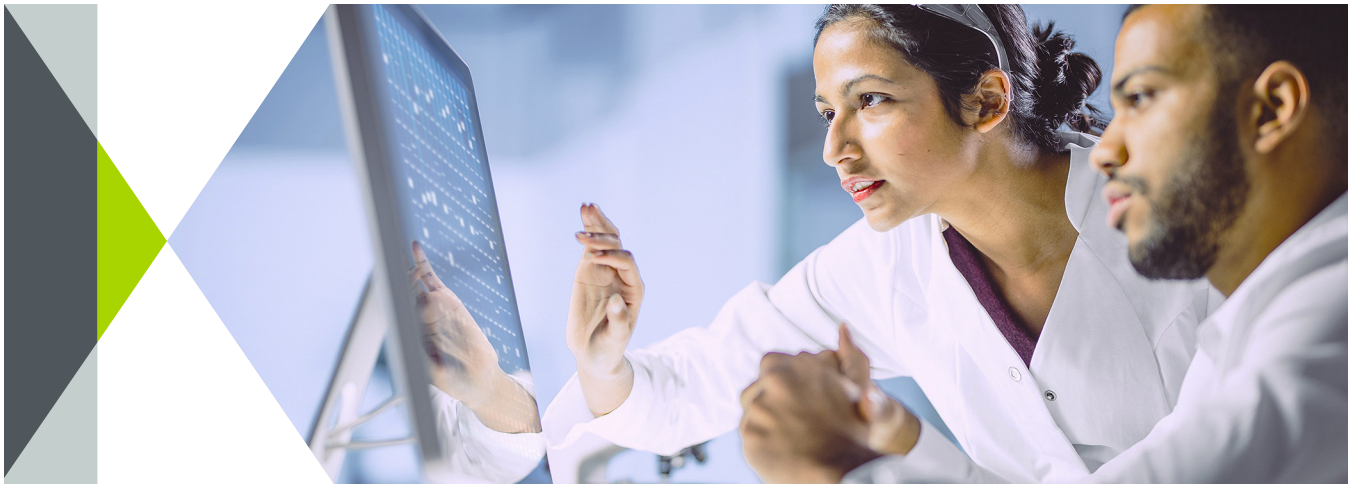


EXECUTIVE INSIGHTS

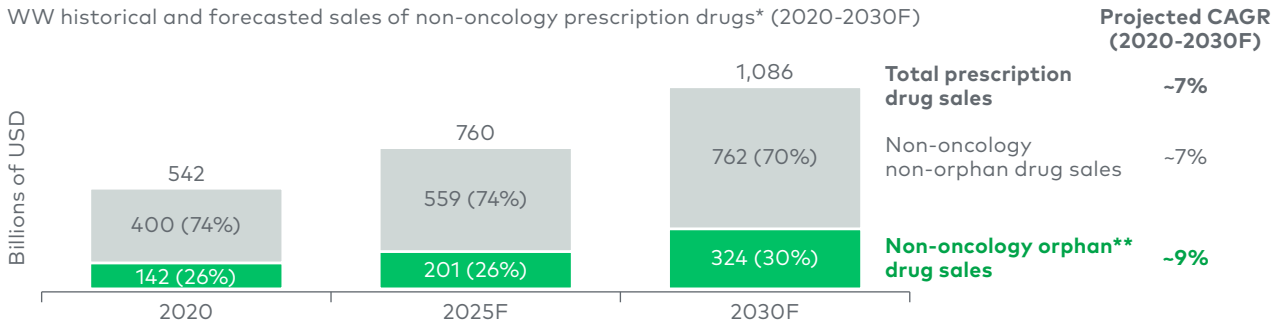
Opportunities for Rare Diseases to Drive Growth in Big Pharma

Rare disease is not rare. Over 30 million Americans, or approximately 10% of the country, are affected by diseases with patient populations less than 200,000, according to the U.S. Food and Drug Administration (FDA). These diseases number over 7,000, many are life-threatening and the majority have no approved treatment.

The Orphan Drug Act of 1983 established incentives that transformed rare diseases from neglected conditions into a strategic growth area for the industry. In 2024, 26 of CDER's 50 novel approvals (52%) carried orphan designations (oncology and non-oncology). Non-oncology orphan drugs are projected to contribute nearly one-third of global prescription sales by 2030 at $324 billion, outpacing the growth of the broader pharma market (see Figure 1) and totaling revenues on par with the gross domestic product of countries such as Finland,

Figure 1

Non-oncology orphan drug market growth and average and median revenues



*Includes marketed and pipeline branded products but not generics
**Orphan drug categorization based on presence of at least one rare disease indication
Note: WW=worldwide; CAGR=compound annual growth rate
Source: EvaluatePharma data (July-August 2025)

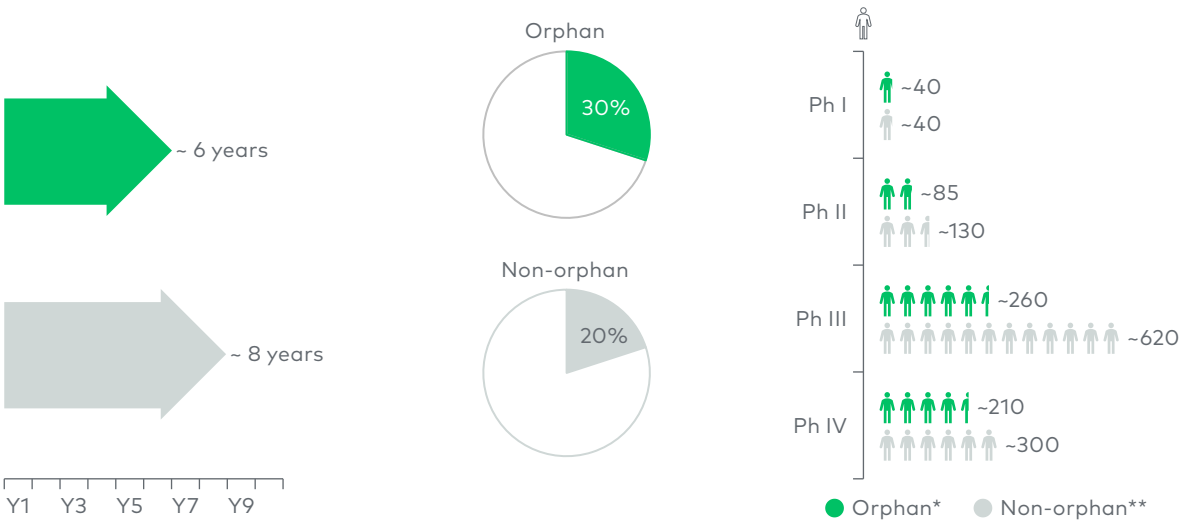
Chile and Portugal. Importantly, non-oncology orphan indications have become of strategic importance to large-cap biopharma, with revenues projected to reach over $100B in sales by 2030F across the top 15 pharma (over 13% of their total 2030F sales) and signaling increasing relevance to their long-term growth.

Advantages in orphan markets

Participation in orphan disease markets may offer biopharma companies uniquely advantaged models for value creation given their potential for relative capital efficiency (see Figure 2). The key drivers underpinning this potential for a favorable risk-reward profile include:

- **Clinical development efficiency:** Clinical programs are typically lean, with pivotal trials often enrolling about 60% fewer patients in Phase III trials vs. non-orphan drugs, reducing both cost and time-to-market and improving ROI.
- **Higher probability of success:** Orphan assets demonstrate meaningfully higher development success rates, with an overall likelihood of approval from Phase I of roughly 30% compared to approximately 20% for non-orphan programs. This is because they frequently target well-validated biology, yield larger effect sizes in enriched populations, benefit from regulatory flexibility and are conducted at concentrated centers of excellence with engaged patient networks.
- **Regulatory advantages:** Specialized FDA guidance (e.g., on trial design and endpoints) and flexibility (e.g., acceptance of surrogate endpoints and single-arm or adaptive clinical designs) can streamline the regulatory process and are complemented by incentives such as priority review vouchers.
- **Policy environment:** The One Big Beautiful Bill Act has expanded the Inflation Reduction Act's orphan drug exemption, allowing multi-indication rare disease products to remain insulated from Medicare price negotiations. The negotiation eligibility for orphan drugs that later gain non-rare disease indications now begins at the non-orphan approval date, thereby delaying exposure.
- **Competitive insulation:** First-in-class therapies typically retain a strong leadership position, often maintaining greater than a 60% share five years post-launch. Across launched non-oncology drugs, rare disease indications average around four marketed therapies per disease, compared to approximately nine for non-rare indications.
- **Commercial infrastructure:** Orphan patient populations are often concentrated within a limited number of centers of excellence, enabling high-touch patient services and smaller field teams.

Figure 2
Benefits of being an orphan asset (excluding oncology)



Quicker approval time	Higher PTRS	Smaller trial sizes across phases

*Average time from IND filing to approval for top 40 revenue-generating orphan drugs launched in the U.S. from 2015 to 2024
**Weighted average across therapeutic areas (excluding oncology) of time from IND filing to approval for 220 novel therapeutics launched from 2015 to 2022 (Wong et al., 2023)
***Probability of success from Ph1 to approval for orphan and non-orphan drugs averaged across non-oncology indications
^Average patient accrual by trial phase for orphan and non-orphan drugs, based on an analysis of ~24K clinical trials
^^Orphan drugs approved for a single rare condition are shielded from Medicare price negotiations under the Inflation Reduction Act — helping preserve pricing flexibility and investment incentives for rare disease therapies
^^^Based on Health and Human Services and Centers for Medicare & Medicaid Services negotiated prices off of the 2023 list price for the 10 drugs selected in the first negotiation cycle
Note: IND=investigational new drug; PTRS=probability of technical and regulatory success
Source: [1]PharmaProjects (2025); [2]EvaluatePharma data (July 2025); [3]Wong et al., JAMA (2023); [4]MIT Project Alpha (2025Q2); [5]TrialTrove (2024); FDA (2025); Congress.gov

Despite these potential advantages, it is important to note that these are not universal and do not guarantee success. While there can be multiple advantages in pursuing rare diseases, these can attenuate in indications lacking natural histories or validated endpoints, or where effective SoCs force active comparator trials. Participation in orphan disease does not guarantee success. Indeed, success can breed competition and erode expected advantages.

Proven success stories and drivers

While historically viewed as niche, some orphan drugs have demonstrated blockbuster, and even mega-blockbuster, success. Advances in precision biology, life cycle expansion and patient access have enabled several therapies to achieve multibillion-dollar revenues, reshaping expectations for the commercial scale of rare disease products. While the largest non-orphan blockbusters boast larger top lines than the largest orphan assets, the average of the top 50 orphan products still reaches $1.7 billion. Some analyses suggest that on a per-indication comparison, orphan assets are on par with those of non-orphan assets. As of 2024, one orphan therapy surpassed $10 billion, another delivered $5 billion and 18 others have achieved more than $1 billion in annual sales.

These blockbuster orphan drugs tend to share a common set of attributes that have enabled their success (Figure 3 shows four examples), via:

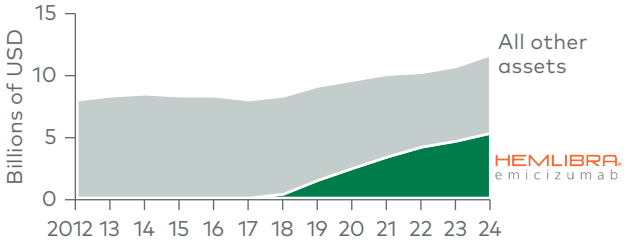
- Redefining standards of care by delivering **transformative efficacy and safety**. For example, Trikafta, Vertex's therapy for cystic fibrosis (CF), revolutionized treatment by delivering substantially improved FEV, exacerbations and QoL over prior doublets, enabling greater treatment duration and use. Trikafta also showed benefit across a wider range of genotypes and age groups, expanding the addressable population to cover most CF patients.
- Applying **disciplined life cycle expansion** to broaden reach over time. For example, Alexion expanded Soliris and Ultomiris applicability both across rare indications (PNH, aHUS, gMG and NMOSD) and within indications (e.g., expanded eligibility and dosing advantages for higher uptake).
- Providing **convenient administration** accelerates uptake and adherence. For example, Hemlibra replaced frequent IV infusions with subcutaneous prophylaxis while enhancing bleed control in both inhibitor and non-inhibitor patients.
- Finally, enabling **robust patient identification and activation** amplifies market impact: Vyndaqel, Amvuttra and Attruby are unlocking a largely undiagnosed transthyretin amyloidosis population through investment in genetic testing, diagnostic programs and advocacy engagements.

Given the association of many orphan success stories, these attributes could provide the foundation for the next wave of orphan innovation.

Figure 3
Example leading rare disease franchises and key products

Hemophilia A

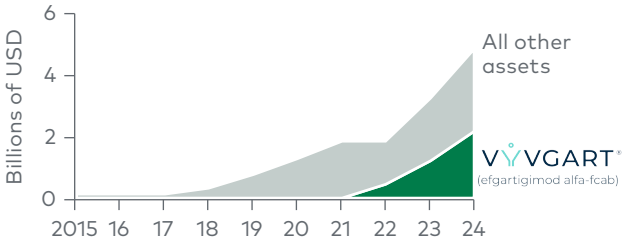
Worldwide branded sales,* hemophilia A
2012-2024



- Shifted SoC from management to prophylactic treatment, **increasing per-patient value**
- Hemlibra enabled prophylaxis in young patients, **expanding addressable patients**

Myasthenia Gravis

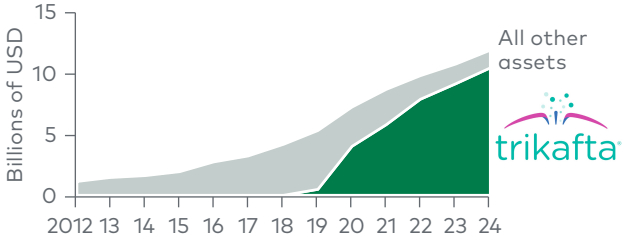
Worldwide branded sales,* myasthenia gravis
2015-2024



- Indication **expansion grew the addressable market**, from ultra-rare to gMG or gMG to broader use
- Shifted care from reactive rescue therapies to remission maintenance, **increasing per-patient annual cost**

Cystic Fibrosis

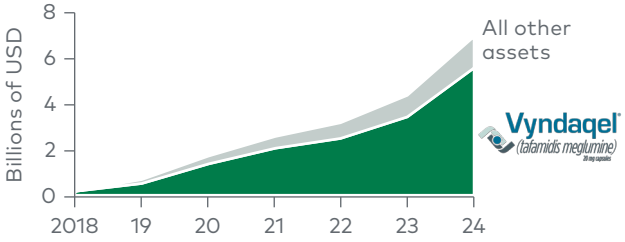
Worldwide branded sales,* cystic fibrosis
2012-2024



- Launched genotype-specific and broadened to encompass additional mutations, **expanding the treatable population**
- Trikafta drove SoC from fragmented monotherapies to triplet therapy resulting in **near-universal brand share**

Amyloidosis

Worldwide branded sales,* amyloidosis
2018-2024



- Drove diagnostic expansion/patient identification efforts, resulting in **increased awareness and market size**
- As a first-in-class therapy, Vyndaqel promoted **high-cost, long-term use of therapy** rather than reactive treatment

*Estimated indication-specific worldwide revenues from EvaluatePharma
Note: gMG = Myasthenia gravis
Source: L.E.K. analysis of EvaluatePharma data (August 2025)

Future opportunities

Orphan investment has exploded over the past approximately 10 years and is primed for continued growth. There are currently about 1,500 drugs in development for rare diseases worldwide, up from just about 800 in 2015. Dozens of orphan therapies are expected to reach the market in the next five years.

Applying learnings from prior success to a simple scan of the orphan pipeline helps develop hypotheses on potential future meaningful opportunities. These include indications such as IgA nephropathy, Von Willebrand disease, primary biliary cholangitis and Charcot-Marie-Tooth

disease, among others (see Figure 4). Each of these areas exhibits similar hallmarks that enabled prior orphan blockbusters: high unmet need resulting in the potential for transformative efficacy and safety, strong patient activation potential and scalable infrastructure. While the quality of the assets has not been evaluated as part of this assessment, the breadth of the pipeline and characteristics of the indications being pursued suggest that the orphan space is poised for continued growth.

Figure 4
Examples of future orphan drug opportunities

Therapeutic Area	Indication*	U.S. addressable population	Competitive intensity**	Potential for transformative efficacy	
			Overall assets	Clearly defined biology***	Significant unmet needs
Kidney	Alport syndrome	3		✓	✓^
Hematology	Autoimmune hemolytic anemia	2.5		✓	✓
	Von Willebrand disease	5.5		✓	✓
Immunological	Primary sclerosing cholangitis	1.5		✓	✓
Musculoskeletal	Myotonic muscular dystrophy	3		✓	✓
Neurological	Charcot-Marie-Tooth disease	5.5		✓	✓
	Fragile X syndrome	3.5		✓	✓
Sensory	Stargardt's macular dystrophy	4		✓	✓
Nephrology	IgA nephropathy	7.5		✓	✓^

Addressable population
= 25K people

Competition intensity (clinical pipeline)
Low (≤ 5 assets) Moderate (6-10 assets) Strong (>10 assets)

*Indications with at least 10K U.S. estimated prevalence (2025)
**Based on number of clinical assets in development
***Clearly defined disease-causing mechanism that can be specifically acted upon by potential therapies (e.g., enzyme, receptor, immune or gene target)
^Recently (2021-24) approved targeted therapy available
Source: PharmaProjects; Orphanet; Datamonitor

Realizing the potential in these emerging indications will require the following:

- **Deliver transformative efficacy:** Build unequivocal evidence of a step-change in efficacy across endpoints routinely accepted as establishing durable benefit in as wide a patient population as possible.
- **Clearly define epidemiology:** Reliable prevalence data is critical and companies that invest early in clarifying disease epidemiology create the foundation for both payer negotiations and patient advocacy engagement.

- **Systematically find patients:** Successful companies are deploying multi-pronged approaches to resolve diagnostics bottlenecks, including genetic testing, AI-driven EMR mining and specialist education to uncover untreated and undertreated populations.
- **Articulate residual unmet need:** Even in conditions with existing therapies, residual gaps (durability, administration burden, partial efficacy) must be clearly documented (e.g., patient-reported outcomes are particularly powerful in demonstrating quality-of-life improvements).
- **Build a robust HEOR evidence base:** As orphan drugs expand toward meaningful patient populations, payers are likely to demand evidence of reduced or eliminated downstream costs, exacerbating the need to quantify avoided hospitalizations, productivity loss and long-term complications.
- **Engage stakeholders early:** Proactive dialogue with regulators, payers and advocacy groups, including co-developing trial endpoints with regulators and collaborating on diagnostic infrastructure, can potentially accelerate adoption and support favorable coverage.

Together, these imperatives can define a repeatable model to successfully capture the opportunity in orphan drugs.

Overall outlook

The orphan drug segment is likely to remain one of the most attractive growth areas in pharma. Potential for structural advantages, resilient demand and emerging indications point toward further expansion. While policy scrutiny is likely to continue, orphan assets remain comparatively advantaged and continue to attract both investor and strategic interest.

For pharma leaders, the opportunity lies not only in scientific innovation but also in systematic market development, from patient-finding to downstream value demonstration. Companies that integrate these elements are likely to be best positioned to capture the next wave of growth in orphan drugs.

For more information, please contact us.

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