# ORPHAN DRUG REPORT 2022

By Melanie Senior and Andreas Hadjivasiliou | APRIL 2022

Evaluate

# Orphan drug report 2022
# Niche no longer

Orphan drug sales growth continues to outpace that of the wider pharmaceuticals market. These products are no longer niche; over half of FDA's 2021 approvals were orphan drugs intended to treat rare diseases*. By 2026, orphans will make up a fifth of all prescription drug sales, and almost a third of the global drug pipeline's value.

Big pharma have long woken up to this reality. They will book sales for nine of the top ten best-selling orphan drugs in 2026 – assuming Vertex isn't acquired in the meantime. By then, almost 40% of Johnson & Johnson's pharmaceutical sales will come from orphans, thanks largely to blood cancer drugs Imbruvica and Darzalex, which are expected to bring in over $23 billion in combined sales. (AbbVie co-promotes Imbruvica in the US.)

> Each of the top ten orphans in 2026 will be worth between $3 billion and $13 billion.

The rise of orphan blockbusters – each of the top ten orphans in 2026 will be worth between $3 billion and $13 billion – continues to drive calls to reform the 40 year old US Orphan Drug Act and the European Union's 1999 **Orphan Regulation**. The pandemic stalled most legislative action, but there are signs of reimbursement push-back in Europe's biggest market, Germany.

The orphan drug sector is unlikely to lose steam, however. Despite its rapid growth, many of the estimated 7000 rare diseases remain under-served. And as other diseases are better understood and sliced into narrower sub-categories, they are more likely to meet the criteria for a rare condition. Most new drug modalities - gene and cell therapies, gene-edited medicines – first make their mark in rare diseases, for valid scientific and medical reasons. Genetic diseases tend to be relatively uncommon; so, fortunately, do some late-stage refractory cancers.

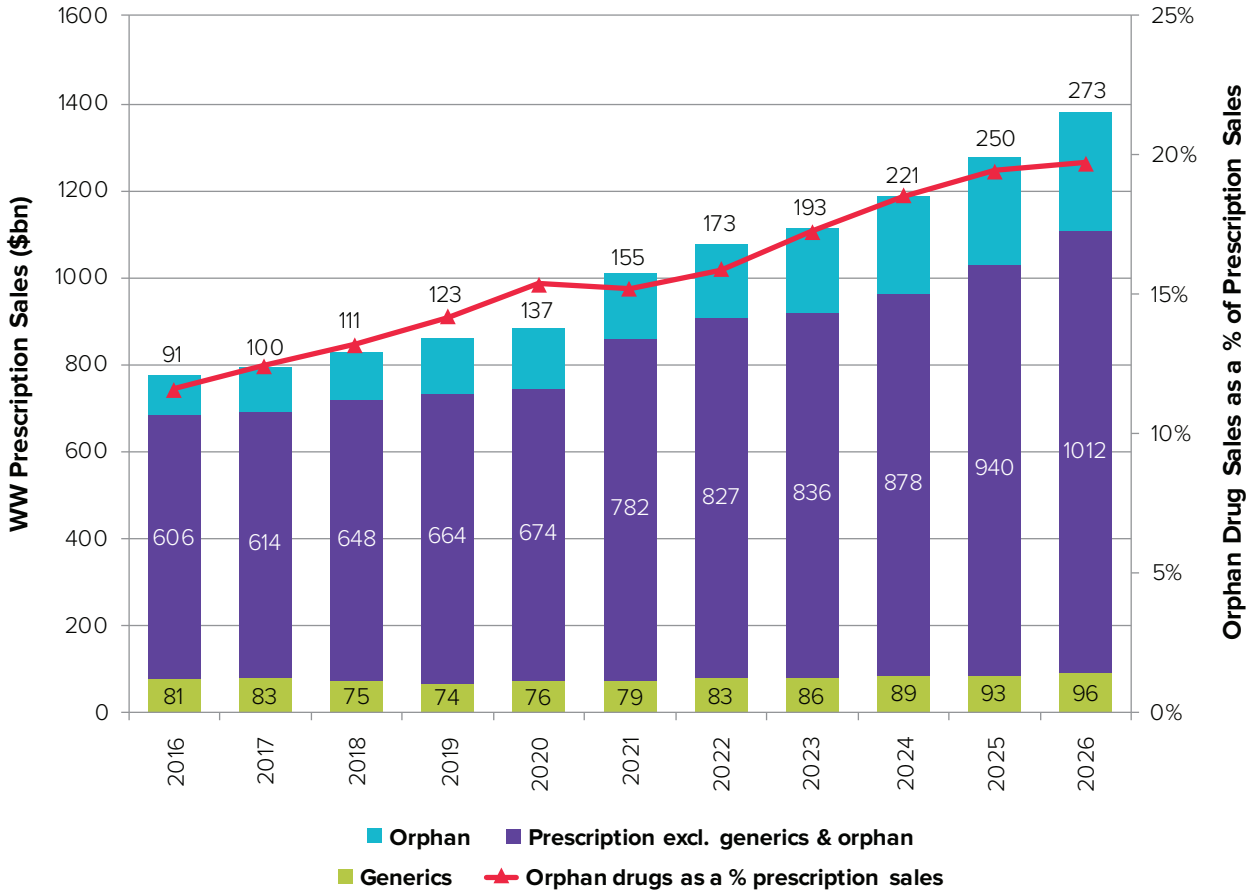
The pharma R&D pipeline is packed with next-generation CAR-T cell therapies, gene therapies, targeted cancer drugs and other new modalities – many with orphan designations. The net present value of forecast 2026 sales of the top ten pipeline orphan drugs is more than $42 billion.

*See Appendix for definitions, what constitutes a 'rare disease', orphan incentives etc.

## Orphan drug sales growth continues to outpace the wider market

The orphan drug market is growing over twice as fast as the non-orphan market, with 2021-2026 CAGR at 12%. By 2026, orphan drug sales will account for 20% of all prescription drug sales.

**FIGURE 1: Worldwide Orphan Drug Sales & Share of Prescription Drug Market (2016-26)**




Source: EvaluatePharma® (February 2022)

In 2021, over half of FDA's Center for Drug Evaluation and Research (CDER) approvals had orphan designation – as did both CAR-T cell therapies approved by the Center for Biologics Evaluation and Research (CBER). New medicines for chronic, widespread conditions such as diabetes, heart or kidney disease are now a minority. FDA approved four rare disease drugs in the first two months of 2022, and just three for non-rare conditions.

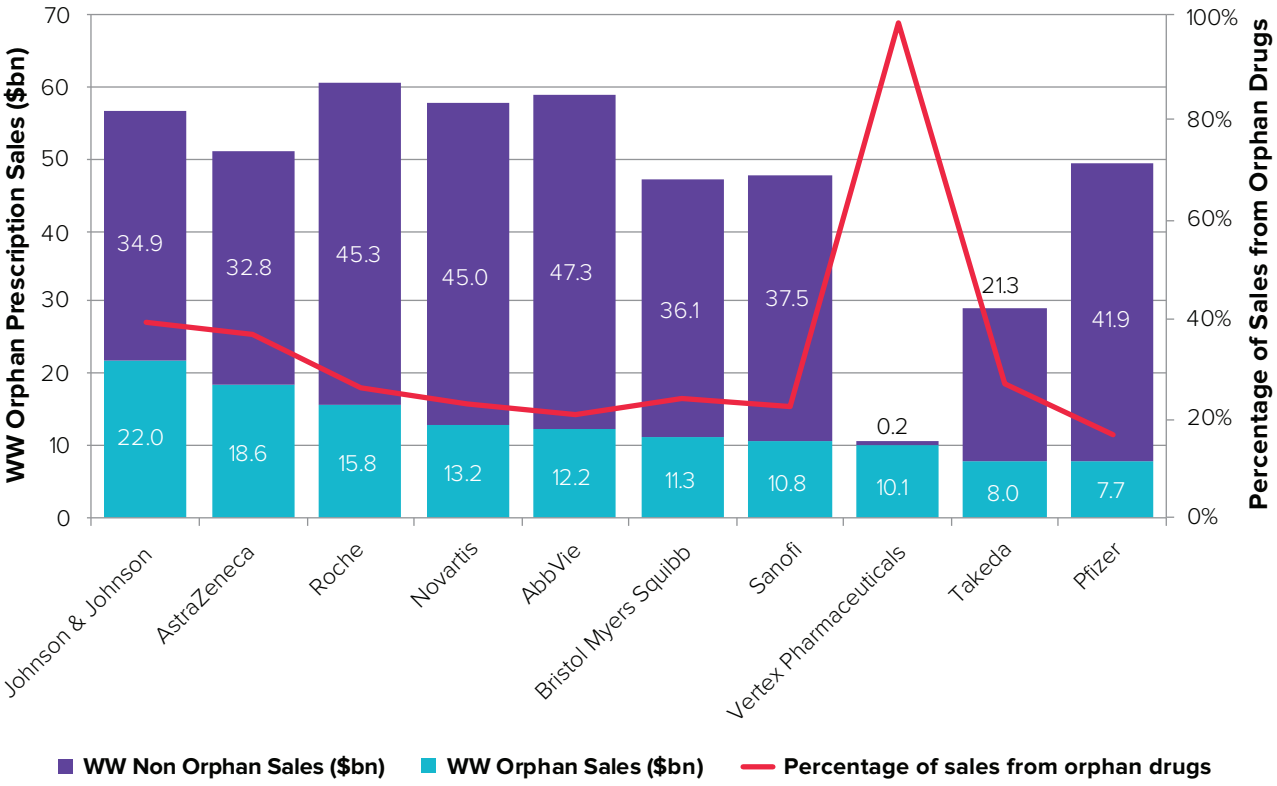
In 2021, over half of FDA's Center for Drug Evaluation and Research (CDER) approvals had orphan designation.

## Big pharma is increasingly reliant on orphans

As orphan drugs graduate from niche to mainstream and reach blockbuster heights, big pharma have adopted and embraced them – just as they did with biologics two decades ago.

In 2026, big pharma will sponsor eight of the top-ten best-selling orphan drugs – nine including Novartis' ex-US rights to Incyte's Jakafi. Vertex will be the only biotech in the top ten, following Alexion's $39 billion acquisition by AstraZeneca in 2021 and Celgene's acquisition by Bristol Myers Squibb for $74 billion in 2019.

**FIGURE 2: Worldwide Orphan Drug Sales (2021/2026): Top 10 Companies & Total Market**




| | | Worldwide orphan sales ($bn) | | | WW non orphan sales ($bn) | | Percentage of sales from orphan drugs | |
|---|---|---|---|---|---|---|---|---|
| Rank | Company | 2021 | 2026 | CAGR | 2021 | 2026 | 2021 | 2026 |
| 1 | Johnson & Johnson | 13.0 | 22.0 | +11,0% | 39.4 | 34.9 | 25% | 39% |
| 2 | AstraZeneca | 6.7 | 18.6 | +22,6% | 28.7 | 32.8 | 19% | 36% |
| 3 | Roche | 10.1 | 15.8 | +9,3% | 39.1 | 45.3 | 21% | 26% |
| 4 | Novartis | 13.7 | 13.2 | -0,8% | 37.4 | 45.0 | 27% | 23% |
| 5 | AbbVie | 7.8 | 12.2 | +9,4% | 46.6 | 47.3 | 14% | 20% |
| 6 | Bristol Myers Squibb | 22.0 | 11.3 | -12,5% | 23.6 | 36.1 | 48% | 24% |
| 7 | Sanofi | 7.0 | 10.8 | +8,9% | 31.7 | 37.5 | 18% | 22% |
| 8 | Vertex Pharmaceuticals | 7.2 | 10.1 | +7,1% | 0.0 | 0.2 | 100% | 98% |
| 9 | Takeda | 6.7 | 8.0 | +3,3% | 23.0 | 21.3 | 23% | 27% |
| 10 | Pfizer | 5.1 | 7.7 | +8,6% | 65.1 | 41.9 | 7% | 16% |

Source: EvaluatePharma® (February 2022)

By 2026, nearly 40% of Johnson & Johnson's pharma sales will come from orphan drugs. They'll make up over a fifth of sales at seven other big pharma.

J&J will have displaced BMS from the 2024 top orphan-seller spot by 2026, as patents expire this year on BMS' blockbuster orphan Revlimid, which came from Celgene.

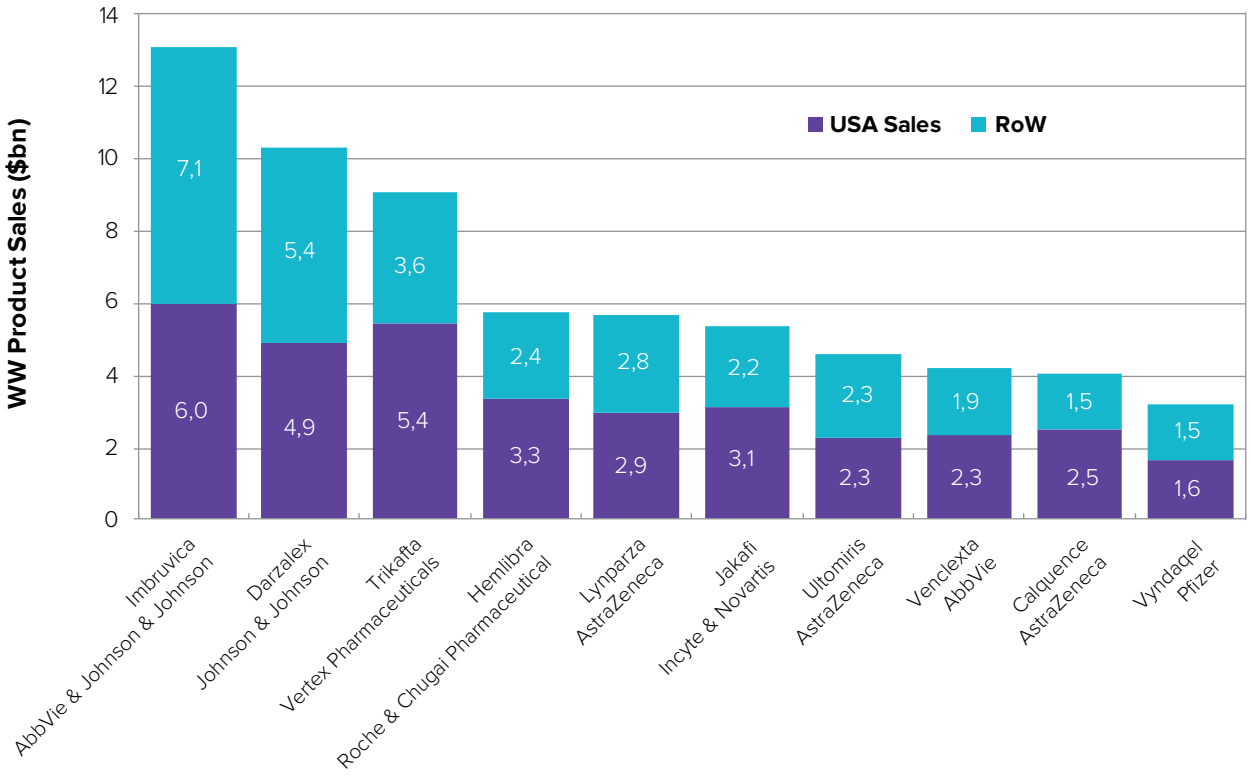
AstraZeneca will take silver thanks to Alexion, while oncology-focused Roche and its Swiss neighbour Novartis maintain third and fourth.

AstraZeneca's 22.6% forecast CAGR between 2021-2026 – powered by Alexion - is more than double the next best, Johnson & Johnson's 11%. BMS' expected -12.5% CAGR over the period is due to declining sales of Revlimid, which generated $12.8 billion in 2021.

## Orphans out-size mass market drugs

Whether cause or consequence of big pharma's involvement (or a bit of both), orphan drugs are forecast to out-size several mass market drugs for chronic, widespread diseases.

**FIGURE 3: Top 10 Selling Orphans by Worldwide Sales 2026**




Source: EvaluatePharma® (February 2022)

**FIGURE 4: Top 10 Selling Orphan Drugs in the World**

| Rank | Product | Mechanism of Action | Therapeutic Category | Therapeutic Subcategory | Company |
|---|---|---|---|---|---|
| 1 | Imbruvica | Bruton's tyrosine kinase (BTK) inhibitor | Oncology | Protein kinase inhibitors | AbbVie & Johnson & Johnson |
| 2 | Darzalex | Lymphocyte differentiation antigen CD38 antibody | Oncology | Other cancer treatments | Johnson & Johnson |
| 3 | Trikafta | Cystic fibrosis transmembrane conductance regulator (CFTR) potentiator; Cystic fibrosis transmembrane conductance regulator (CFTR) regulator | Respiratory | Other respiratory agents | Vertex Pharmaceuticals |
| 4 | Hemlibra | Coagulation factor IXa antibody; Coagulation factor X antibody | Blood | Anti-fibrinolytics | Roche & Chugai Pharmaceutical |
| 5 | Lynparza | Poly (ADP-ribose) polymerase (PARP) inhibitor; Poly (ADP-ribose) polymerase 1 (PARP1) inhibitor; Poly (ADP-ribose) polymerase 3 (PARP3) inhibitor | Oncology | Other cancer treatments | AstraZeneca |

| Rank | Product | Mechanism of Action | Therapeutic Category | Therapeutic Subcategory | Company |
|---|---|---|---|---|---|
| 6 | Jakafi | Janus kinase 1 (JAK1) inhibitor; Janus kinase 2 (JAK2) inhibitor | Oncology | Protein kinase inhibitors | Incyte & Novartis |
| 7 | Ultomiris | Complement factor C5 antibody | Blood | Other haematologicals | AstraZeneca |
| 8 | Venclexta | B-cell lymphoma 2 (BCL-2) inhibitor | Oncology | Other cancer treatments | AbbVie |
| 9 | Calquence | Bruton's tyrosine kinase (BTK) inhibitor | Oncology | Protein kinase inhibitors | AstraZeneca |
| 10 | Vyndaqel | Transthyretin (TTR) dissociation inhibitor | Central Nervous System | Other CNS drugs | Pfizer |

Note: Sales represent company reported sales where available, otherwise based on an average of equity analyst estimates.
All sales analysis based on EvaluatePharma®'s clean 'Orphan' sub-set of products, as defined in the Overview section.

Source: EvaluatePharma® (February 2022)

AbbVie/J&J's chronic lymphocytic leukemia (CLL) drug Imbruvica (ibrutinib) will top the orphan drug table in 2026, with $13 billion in worldwide sales - rivalling BMS/Pfizer's mass-market blood thinner, Eliquis (apixaban) and Sanofi's anti-inflammatory Dupixent (dupilumab), two of the top selling drugs globally.

Number two orphan Darzalex (daratumumab), sold by J&J for multiple myeloma, is expected to reap $10 billion in 2026, topping Novo Nordisk's diabetes best-seller Ozempic (semaglutide) and AbbVie's rheumatoid arthritis drug Rinvoq (upadacitinib). An estimated 35,000 people are diagnosed with multiple myeloma each year in the US. Diabetes affects one in ten Americans – almost 40 million.

Widening the lens to the top twenty best-selling orphan drugs in 2026 brings just two more biotechs into the picture: Argenx, with Vyvgart (efgartigimod alfa) for myasthenia gravis (ranked 14) and Seagen with Adcetris (brentuximab) for lymphoma (ranked 15).

## Blood cancers lead orphan charge

Liquid cancers account for lion's share of top ten orphans in 2026. Blood cancers are difficult to treat, in part because they are not localised like most solid tumors. Blood cancers are also the most common cancers in children, though some subtypes, like acute myeloid leukemia, affect older adults.

> Five of the top ten 2026 orphans – representing over half (56%) the combined $65 billion sales - address blood cancers.

Five of the top ten 2026 orphans – representing over half (56%) the combined $65 billion sales - address blood cancers. They include Imbruvica (ibrutinib), Darzalex (daratumumab), Venclexta (venetoclax), Calquence (acalabrutinib) and Jakafi (ruxolitinib), which treats rare bone marrow cancers myelofibrosis and polycythemia vera.

Two others in the top ten treat other rare blood disorders: Roche's Hemlibra addresses haemophilia A, a blood clotting disorder, and AstraZeneca's Ultomiris (ravulizumab) is used for paroxysmal nocturnal haemoglobinuria (PNH) and atypical haemolytic uremic syndrome (aHUS).

## Orphan drugs face growing competition

Orphans' strong growth is leading to crowding in some corners of the market. As discussed above, the top ten orphan drugs in 2026 include three that address chronic lymphocytic leukemia. Two of them – Imbruvica and AstraZeneca's newer Calquence – share the same mechanism of action: they both inhibit Bruton's tyrosine kinase, though Calquence is dubbed next-generation due to reportedly greater potency and selectivity, which makes it more tolerable. AbbVie and ex-US marketing partner Janssen hope to defend Imbruvica, including by combining it with another top ten orphan, AbbVie/Roche's BCL-2 inhibitor Venclexta. A combination study in CLL showed positive results at ASCO 2021.

As AbbVie continues to face biosimilar competition to best-selling non-orphan Humira (2021 sales: $21 billion), it is counting on its CLL orphan duo, plus a non-orphan drug, the anti-inflammatory Rinvoq (upadacitinib), to fill the gap.

## Line extension strategies, non-orphan style

Greater competition is driving the kind of line extension behaviour seen in non-orphan spaces, such as new formulations and more convenient dosing. This is good news for patients.

AstraZeneca / Alexion's Ultomiris is a longer-lasting version of the company's top ten orphan veteran Soliris (2021 combined sales: $4.1bn), infused every 8 weeks rather than fortnightly. It faces competition from Apellis' Empaveli (pegcetacoplan), approved in 2021 for the same rare blood disorder, paroxysmal nocturnal haemoglobinuria. Yet Ultomiris, also approved for atypical haemolytic uremic syndrome, broke the $1bn mark in 2020, up by over 200% compared to the previous year. It is in late-stage trials for two other neurological conditions, myasthenia gravis and neuromyelitis optica spectrum disorder (NMOSD) and two nephrology conditions. A sub-cutaneous formulation is also in the works. By 2026, Ultomiris sales are expected to top $4.5 billion.

Similarly, Pfizer's Vyndaqel (tafamidis) may have to share the stage in cardiomyopathy caused by transthyretin-mediated amyloidosis (ATTR), a multi-system disease resulting from build-up of an abnormal transport protein. Alnylam's RNAi-based drug Onpattro (patirsiran) and Ionis' Tegsedi (inotersen) are already approved for polyneuropathy associated with amyloidosis; Onpattro is being tested in the larger cardiomyopathy indication (ATTR-CM) and Alnylam has also filed its longer-lasting follow-on drug, vutrisiran, for polyneuropathy associated with amyloidosis. Vutrisiran is injected just four times a year, rather than the three-weekly dosing required for Onpattro.

AstraZeneca also has a horse in the ATTR race, since its **December 2021 deal** with Ionis for the Phase 3 ligand-conjugated antisense medicine eplontersen.

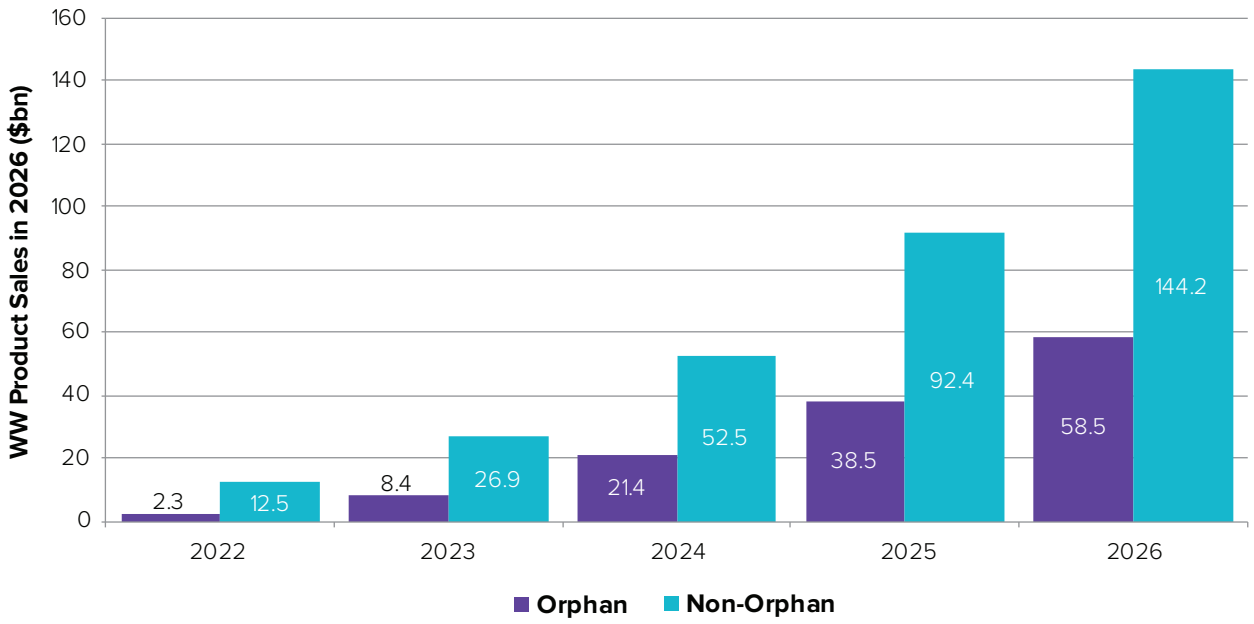
These dynamics are driving greater awareness of the condition, while improved diagnostic tools help uncover more cases of ATTR. This in turn **calls into question** ATTR's status as a rare disease – one affecting fewer than 200,000 patients in the US. Pfizer has come under fire for pricing its drug, Vyndaqel, at $225,000 per annum. The price is half that of Onpattro and Tegsedi (approved in smaller indications), but nevertheless way over the cost-effectiveness threshold, according to a study in **JAMA Cardiology**. The England and Wales cost-watchdog NICE turned down the drug for reimbursement in 2021.

## Orphans' share of global pipeline grows

Orphans' share of global R&D pipeline value is expected to jump from 16% in 2022 to 29% just two years later - representing 2026 sales of over $58 billion.

The share will remain steady between 2024 and 2026.

**FIGURE 5: Worldwide: Pipeline of Orphan vs. Non-Orphan Drugs to 2026**




| | WW Sales ($bn) | | | | |
|---|---|---|---|---|---|
| R&D Pipeline | 2022 | 2023 | 2024 | 2025 | 2026 |
| Orphan | 2.3 | 8.4 | 21.4 | 38.5 | 58.5 |
| Non-Orphan | 12.5 | 26.9 | 52.5 | 92.4 | 144.2 |
| % Orphan Sales | 16% | 24% | 29% | 29% | 29% |
| Total | 14.9 | 35.3 | 73.8 | 130.9 | 202.6 |
| Cumulative Orphan | 2.3 | 10.7 | 32.1 | 70.7 | 129.2 |
| Cumulative Non-Orphan | 12.5 | 39.4 | 91.9 | 184.2 | 328.4 |

Note: All sales analysis based on EvaluatePharma®'s 'Orphan' sub-set of products, as defined in the Overview section.

Source: EvaluatePharma® (February 2022)

## A sandbox for new modalities

Many new modalities, such as CAR-T cell therapies and gene-edited therapies, start out in orphan indications, for good reason. These conditions are often genetically defined, under-served, with a poor prognosis. They offer a fast-tracked opportunity to demonstrate proof-of-concept for novel technologies. The explosion in new tools and drug discovery approaches, from gene-editing to AI-powered screening and drug design, is likely to continue to fuel orphans' rise.

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The top twenty orphan R&D products showcase this range of modalities. It includes a stem cell treatment, several cell- and gene- therapies, a CRISPR Cas9 gene-edited therapy, RNAi therapeutics, targeted and bispecific antibodies and even an oral suspension of gold nanocrystals, Clene's CNM-Au8 for ALS.

**FIGURE 6: Top 5 Orphan Drugs in 2026 (Phase III/ Filed) by NPV**

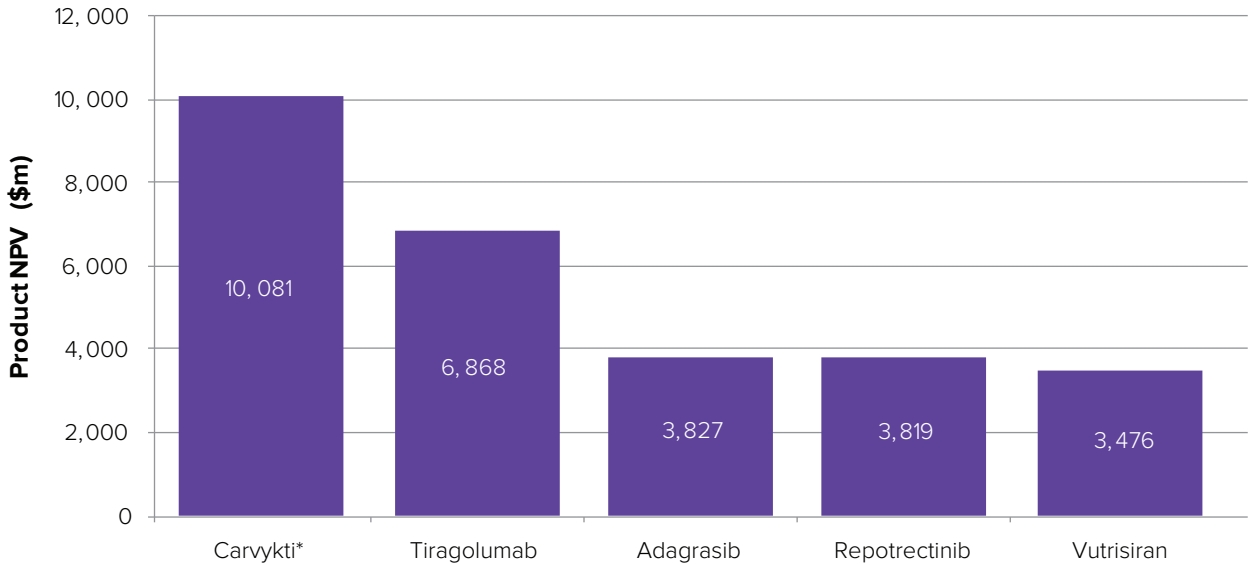



**FIGURE 7: Worldwide Top 5 Orphan R&D Products based on NPV**

| Rank | Product | Company | Phase (Current) | Therapeutic Category | Therapeutic Subcategory | Sales ($m) 2026 | WW NPV | Strategy |
|---|---|---|---|---|---|---|---|---|
| 1 | Carvykti* | Johnson & Johnson | Filed | Oncology | Immuno-oncology | 1,692 | 10,081 | In-licensed |
| 2 | Tiragolumab | Roche | Phase III | Oncology | Other cancer treatments | 1,237 | 6,868 | Organic |
| 3 | Adagrasib | Mirati Therapeutics | Phase III | Oncology | Protein kinase inhibitors | 1,563 | 3,827 | In-licensed |
| 4 | Repotrectinib | Turning Point Therapeutics | Phase III | Various | Other therapeutic products | 1,158 | 3,819 | Organic |
| 5 | Vutrisiran | Alnylam Pharmaceuticals | Filed | Blood | Anti-anaemics | 1,828 | 3,476 | Organic |

Note: Sales represent company reported sales where available, otherwise based on an average of equity analyst estimates. Carvykti approved in February 2022.

Source: EvaluatePharma® (February 2022)

As of February 2022, the most valuable pipeline orphan, with forecast 2026 sales of $1.7 billion and an NPV of over $10 billion, is Johnson & Johnson's CAR-T cell therapy Carvykti (ciltacabtagene autoleucel/'cilta-cel'). This was in fact approved in February 2022 for relapsed or refractory multiple myeloma after four or more prior treatment rounds.

Carvykti is the sixth CAR-T cell therapy to reach the US market, and the second that targets B-cell maturation antigen (BCMA). Its forecast NPV belies the relatively slow sales ramp up for this treatment category to date, due in large part to complex, expensive administration procedures and a high resource burden. Novartis' Kymriah, the first CAR-T to be approved in the US in 2017, sold $587 million in 2021 and is expected to be just below the $1 billion mark by 2026. (2026: $944 million)

CAR-T and gene-edited therapies are still in their infancy today but are expected to accumulate further indications and value as the underlying technologies allow for more efficient, faster administration. They may not reach the heights of Merck's $17.2 billion cancer behemoth Keytruda (pembrolizumab), first approved as an orphan eight years ago, which now has over two dozen approved indications. But with six-figure price tags, several CAR-T cell therapies are expected to reach blockbuster status. Even by 2026, J&J's Carvykti, Gilead Sciences' Yescarta, BMS' duo of Abecma (idecabtagene vicleucel) and Breyanzi – both legacy Celgene products, approved in 2021 – are each forecast to top $1 billion.

> With six-figure price tags, several CAR-T cell therapies are expected to reach blockbuster status.

Vertex/CRISPR Therapeutics' CRISPR Cas9 gene edited therapy CTX001 is also a pipeline lead, with forecast 2026 sales of $1.3bn. It is in development for transfusion dependent beta thalassemia and severe sickle cell disease, both caused by abnormal haemoglobin in red blood cells. The therapy involves editing patients' heamatopoietic stem cells outside the body (ex vivo) to produce high levels of fetal haemoglobin, alleviating the need for transfusions and potentially enabling a one-time functional cure for the conditions.

About half of the top 20 R&D orphans have been developed in-house, but Roche/Chugai is the only big pharma in that category. Carvykti was developed by Legend Biotech, Lilly's haematology drug pirtobrutinib came from its acquisition of Loxo Oncology, Astellas' zolbetuximab anti-cancer antibody was developed by Ganymed, and Sanofi's small interference RNA fitusiran for haemophilia prophlyaxis uses technology developed by Alynlam.

Sanofi has two further drugs for rare diseases under regulatory review. One of those, olipudase alfa, inherited from Genzyme, is the latest example of an enzyme replacement therapy (ERT) – a modality that was instrumental in bringing rare diseases and the commercial value of orphan drugs to pharma's radar screens 20 years ago. Competition played out between Genzyme (acquired by Sanofi in 2011 for $20 billion) and Shire (for which Takeda paid $62 billion in 2018), with ERTs launched for under-treated inherited conditions such as Hunter's, Fabry and Gaucher's disease.

Olipudase is in development for acid sphingomyelinase deficiency (ASMD), a rare and progressive condition that affects fat metabolism inside cells. It is also known as Niemann-Pick disease type A & B and affects about 2000 people across the EU, US and Japan. If approved, it would be the first and only treatment for the condition; 2026 sales are forecast at $204m.

## Cancer dominance continues

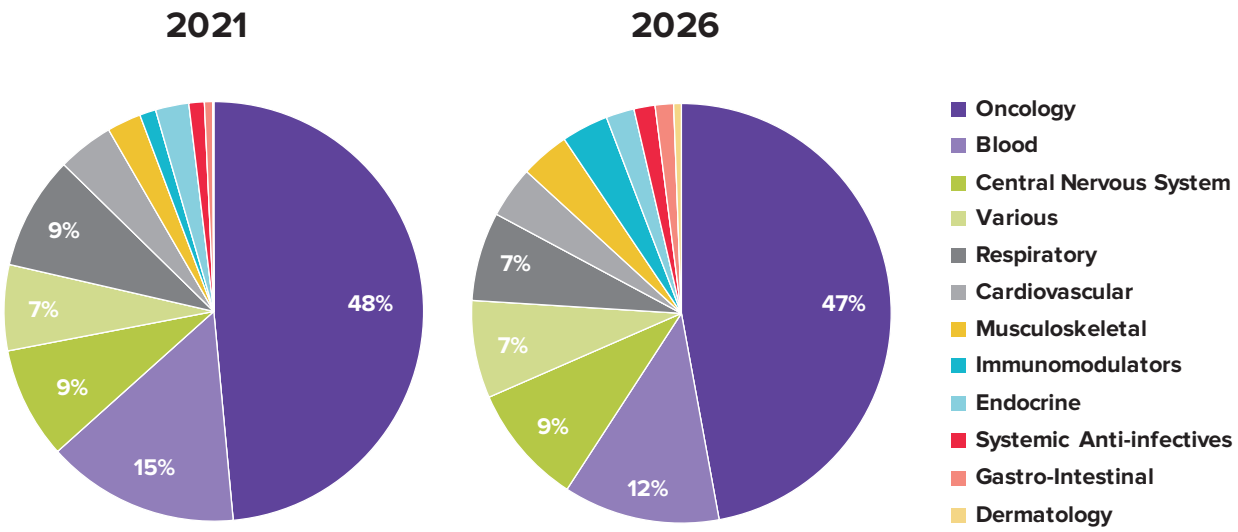
Cancer remains the dominant therapy area for orphan drugs, accounting for six of the top ten pipeline candidates, and two thirds of forecast 2026 sales with a combined NPV of $29.6billion.

**Top 3 therapy areas for orphan drugs**

1. Cancer
2. Blood diseases
3. Central nervous system

Looking across the broader orphan R&D pipeline, blood diseases – including haemophilia and beta thalassemia – are the second most popular therapy area, followed by central nervous system diseases. The top two therapy area rankings are not expected to change between 2021 and 2026; respiratory conditions will cede some ground and the immunomodulators and anti-infectives will grow share.

**FIGURE 8: Share of Worldwide Orphan Drug Sales by Therapeutic Category**




Source: EvaluatePharma® (February 2022)

**FIGURE 9: Worldwide Sales and Lead Company by Therapeutic Category**

| | WW Annual Sales ($bn) | | 2021 | | 2026 | |
|---|---|---|---|---|---|---|
| Therapeutic Category | 2021 | 2026 | Lead Company | WW Sales ($m) | Lead Company | WW Sales ($m) |
| Oncology | 75.1 | 127.5 | Bristol Myers Squibb | 21,457 | Johnson & Johnson | 18,333 |
| Blood | 23.0 | 32.6 | Roche | 3,307 | AstraZeneca | 6,574 |
| Central Nervous System | 13.3 | 25.1 | Biogen | 3,114 | Pfizer | 3,172 |
| Various | 10.2 | 20.4 | Sanofi | 3,841 | Sanofi | 4,544 |
| Respiratory | 13.5 | 18.5 | Vertex Pharmaceuticals | 7,199 | Vertex Pharmaceuticals | 10,125 |
| Cardiovascular | 6.7 | 10.8 | Johnson & Johnson | 3,336 | Johnson & Johnson | 3,173 |
| Musculoskeletal | 4.1 | 10.2 | Sarepta Therapeutics | 617 | Sarepta Therapeutics | 1,978 |
| Immunomodulators | 1.9 | 9.8 | Sanofi | 707 | argenx | 2,445 |
| Endocrine | 4.0 | 5.9 | Novartis | 1,613 | Ascendis Pharma | 1,393 |
| Systemic Anti-infectives | 1.8 | 4.4 | Merck & Co | 650 | AlloVir | 463 |
| Gastro-Intestinal | 1.0 | 3.8 | Takeda | 767 | Takeda | 909 |
| Dermatology | 0.1 | 1.6 | Torii Pharmaceutical | 53 | Krystal Biotech | 807 |

Note: All sales analysis based on EvaluatePharma®'s clean 'Orphan' sub-set of products, as defined in the Appendix section.

Source: EvaluatePharma® (February 2022)

Oncology orphan drug sales will grow 70% between 2021 and 2026 in absolute terms. Sales of orphans treating musculoskeletal disorders, infectious diseases and gastrointestinal conditions will more than double over the period, while immunology and dermatology products will see four-fold and ten-fold growth, respectively.

J&J is the only company expected to lead sales in two categories, oncology (displacing BMS) and cardiovascular disease, where it already leads today. Vertex likewise maintains its leadership in respiratory diseases, thanks to its cystic fibrosis portfolio.

Five biotechs currently appear in 2026's list of lead companies by orphan therapy area, including argenx (immunomodulators) and Sarepta Therapeutics (musculoskeletal). History suggests not all will remain independent for that long.

## Calls to reform Orphan Drug laws

Calls to reform orphan drug legislation continue. The challenge for payers and regulators is that orphan incentives, such as expedited regulatory review and market exclusivity, are applied to drugs that grown to become far larger than the US Orphan Drug Act or EU Orphan Regulation originally envisaged. Developers are also starting to cluster into the same corners, meaning there are now several treatments for certain conditions like PNH, ATTR or myelofibrosis. Patient choice is, of course, welcome – and should, in theory, drive down prices. Greater R&D activity and improved diagnostic tools is also driving awareness of conditions like ATTR. That is good for patients, too, but **calls into question** whether these diseases still qualify as rare (affecting fewer than 200,000 patients in the US).

In the US, the pandemic and politics displaced several regulatory and drug pricing reform plans in 2021. Proposals are on the table to reform FDA's Accelerated Approval pathway, however, which is critical for orphan drugs. These include tighter oversight on post-marketing studies required to determine whether full approval is warranted for 'accelerated' products.

Developers are also starting to cluster into the same corners, meaning there are now several treatments for certain conditions.

The European Union is reviewing its orphan drug framework after **a report published in mid-2020** suggested current versions had not done enough to direct development to areas of unmet need, and that in some rare diseases, the market "looks similar to [that of] standard medicines." Products tend to be developed "in certain more profitable therapeutic areas," the report said. Shorter or variable exclusivity periods are on the table, but although the consultation period has ended, no action has yet been taken.

## HTA pushes back on high-priced orphans

As policymakers consider tweaks to the rules and how much R&D and health system resources should be directed to a few niche indications, health technology assessment agencies are already pushing back. The England and Wales cost-watchdog NICE in 2021 declined to reimburse Pfizer's ATTR drug Vyndaqel due to its price; the drug's US $225,000 per year tag drew criticism for being way over the cost-effectiveness threshold, according to a study in **JAMA Cardiology**.

Germany's cost-watchdog IQWiG also appears ready to clamp down. In a January 2022 press release, the agency called for an end to orphan drugs' exemption from the rigorous cost-effectiveness scrutiny faced by non-orphan medicines. Orphan drugs in Germany are currently assumed to bring some added benefit over existing therapies, without undergoing a full review (until or unless their annual sales exceed €50 million). IQWiG found that this assumption was unjustified in over half of cases analysed since 2011. "It is time to abolish the privilege of fictitious added benefit for orphan drugs!" declares the release.

## Orphan drug growth unlikely to slow

Despite calls for changes to orphan legislation, growth in this sector shows no sign of slowing.

On March 4, 2022 the US regulator **declared** its continued prioritisation of rare diseases, highlighting the growing share of drugs approved to treat rare or orphan conditions. During the first three months of 2022, six of the nine FDA therapy approvals were for rare diseases. Three were in cancer, two in blood disease and one in neurology - broadly in line with the trends discussed above.

**FIGURE 10: FDA (CDER and CBER) Approved Drugs in 2022 (to 18.3.22)**

| Approved Drug | Indication |
|---|---|
| **CDER** | |
| Kimmtrak (tebentafusp-tebn) | Uveal melanoma; cancer of the eye |
| Enjaymo (sutimlimab-jome) | Cold agglutinin disease, a rare kind of anaemia |
| Pyrukynd (mitapivat) | Inherited form of anaemia caused by pyruvate kinase deficiency |
| Vonjo (pacritinib) | Myelofibrosis, a rare bone marrow disorder |
| Ztalmy (ganaxolone) | Seizures associated with cyclin-dependent kinase-like 5 deficiency disorder (CDD), a rare form of genetic epilepsy. |
| **CBER** | |
| Carvykti (ciltacabtagene autoleucel) | Multiple myeloma |

Yet “we must do more,” the agency said, outlining further efforts to support rare disease drug development, including around data collection and sharing, and patient-relevant endpoints. “Despite progress, the vast majority of rare diseases still do not have approved therapies.”

# Appendix

An orphan drug is a pharmaceutical product that treats a rare condition or disease. The development of orphan drugs has been financially incentivised through US law via the Orphan Drug Act of 1983. The National Organization for Rare Disorders (NORD), which was instrumental in establishing the Act, currently estimates that there are as many as 7,000 rare diseases and that up to 30 million Americans suffer from a rare disease. Prior to the 1983 Act, 38 orphan drugs were approved in the United States. The success of the original Orphan Drug Act in the US led to it being adopted in other key markets, most notably in Japan in 1993 and in the European Union in 2000.

## Orphan drug classification methodology

Using publicly available sources, EvaluatePharma® identify products that have been granted orphan drug designations in the US, EU or Japan. These products are then classified as 'EvaluatePharma® orphan drugs' if:

- The product is approved only for use in the indication/s for which it was awarded orphan designation and these indications are covered by Evaluate Pharma®.
- Approximately one-fifth of products have designations in orphan and non-orphan indications. Products that have orphan and non-orphan drug designations and are expected to generate less than 50% of their sales in 2021 and 2026 from their orphan-designated indication/s, are excluded from this analysis. This has led to the exclusion of therapies such as Avastin, Opdivo, Enbrel, Herceptin, Humira and Remicade.
- EvaluatePharma® will also classify R&D products as 'orphan drugs – prior to the products receiving this status from regulatory bodies – in the following cases:
  - The product is being developed in an indication that is classified by regulatory bodies as an orphan disease, and other products for this disease were granted orphan drug designation.
  - The company developing the product states it is seeking orphan drug designation for the product's lead indication.

Evaluate™

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**www.evaluate.com** | **@Evaluate** **@EvaluateVantage**


**Evaluate Headquarters**
Evaluate Ltd.
3 More London
London SE1 2RE
United Kingdom
T +44 (0)20 7377 0800

**Evaluate Americas**
EvaluatePharma USA Inc.
60 State Street, Suite 1910
Boston, MA 02109
USA
T +1 617 573 9450

**Evaluate Asia Pacific**
Evaluate Japan KK
Holland Hills Mori Tower 2F
5-11-2 Toranomon, Minato-ku
Tokyo 105-0001, Japan
T +81 (0)70 4131 0112