

FTI Consulting Inc.
Center for Healthcare Economics and Policy



Quantifying the Value of Orphan Drugs and the Impact of the IRA Sole Orphan Exclusion

Executive Summary

Orphan drugs have had a transformative impact on the lives of patients with rare and often life-threatening conditions. Since the passage of the Orphan Drug Act in 1983, these therapies have improved health outcomes, enhanced quality of life, and extended survival for individuals with a wide variety of diseases: from cystic fibrosis to spinal muscular atrophy to rare cancers. By incentivizing innovation in underserved populations, orphan drugs have filled critical gaps in care, offering hope to millions of patients and their families.

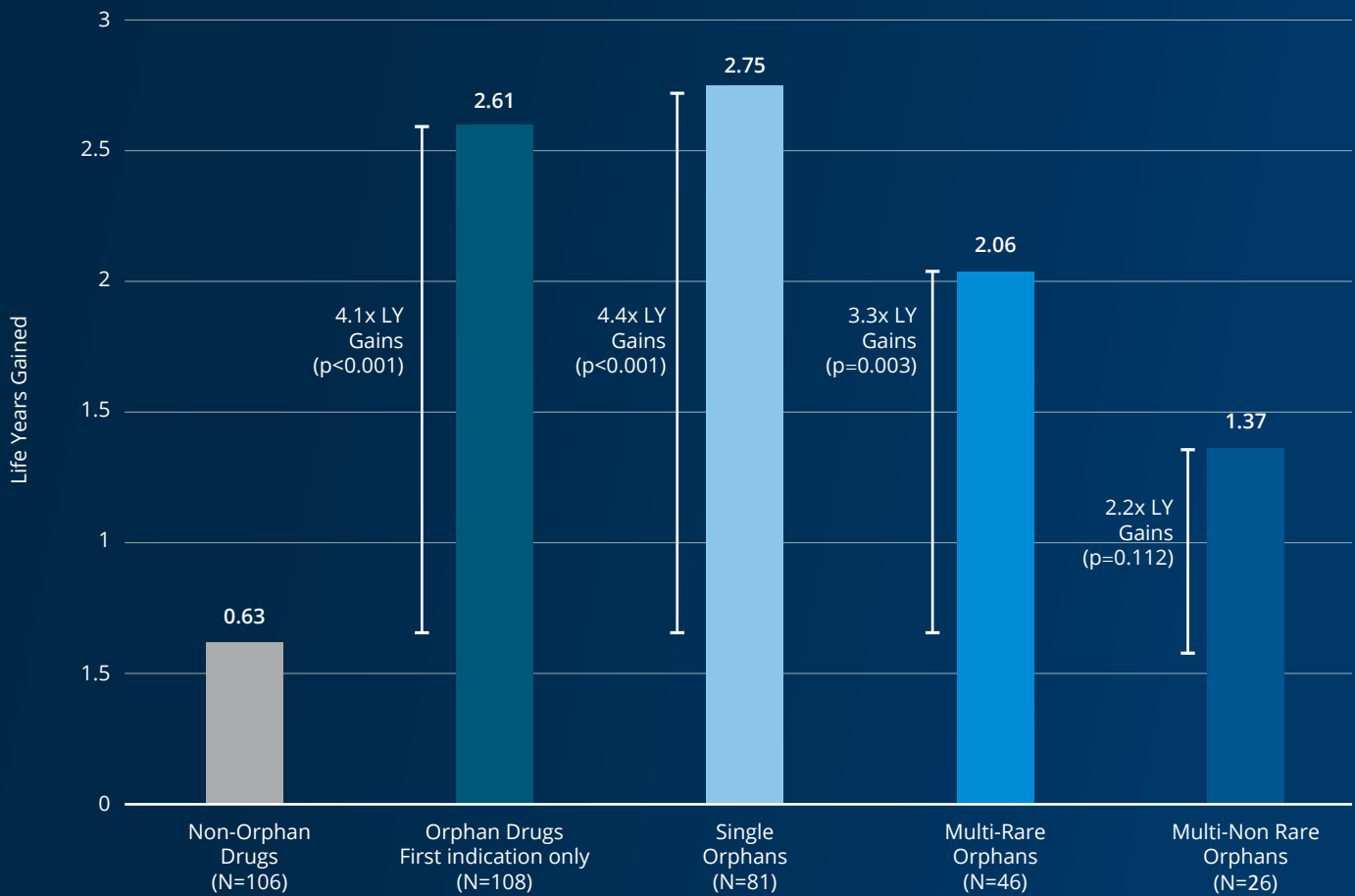
However, the “sole orphan” exclusion under the Inflation Reduction Act of 2022 (IRA) may lead to adverse health outcomes for patients with rare disease. The “sole orphan” exclusion removes drugs from Medicare price negotiation only if they meet a narrow definition of having only one orphan designation. Not only would the sole orphan exclusion discourage the development of new indications for existing orphan drugs, it may make the development of any orphan drug overall less attractive. Although orphan drugs have clearly improved outcomes for patients with rare diseases, the precise magnitude of this impact is yet to be systematically quantified.

This study aimed to estimate the health benefits potentially at risk due to the sole orphan exclusion. We compared the typical health gains—on a per patient basis—for orphan compared to non-orphan drugs. This study found:

- Orphan drugs impact on patient survival is more than **4 times larger** than the survival gains of non-orphan drugs.
- Orphan drugs with multiple rare disease indications provide more than **3 times the survival gains** as non-orphan drugs.
- Because many orphan drugs treat multiple rare and non-rare diseases, removing them from ‘sole orphan’ exclusion, **58% of orphan drugs could be eligible** for Medicare Drug Price Negotiation.
- If the sole orphan exclusion prevented all orphan drugs with multiple indications to be developed, **over 16.7 million life years would be lost** over the next 15 years.

These health gains for patients with rare disease could be at risk if the sole orphan exclusion is not removed and replaced by excluding all orphan drugs, including those that treat multiple diseases, from the Medicare Drug Price Negotiation Program.

Life-Year Gains by Drug Type and Indication Pathway



Notes: The Non-Orphan Drugs bar represents LY gains for the drugs whose first approved indication was for a non rare disease. The Orphan Drugs First Indication Only bar represents the LY gains from the first approved indication among all drugs whose first approved indication was for a rare disease. The Single Orphans bar represents the LY gains of all the orphan drugs with a single indication. The Multi-Rare Orphans bar represents the LY gains of orphan drugs with multiple rare indications. The Multi-Non Rare Orphans bar represents the LY gains of orphan drugs with any non-rare indications.

Table of Contents

Introduction	5
Methodology	6
Findings	8
Finding #1: Orphan drugs impact on patient survival is more than 4 times larger than the survival gains of non-orphan drugs	8
Finding #2: Orphan drugs with multiple rare disease indications provide more than 3 times the survival gains as non-orphan drugs	8
Finding #3: Because many orphan drugs treat multiple rare and non-rare diseases, 58% of orphan drugs could be eligible for Medicare Drug Price Negotiation	9
Finding #4: If the sole orphan exclusion prevented all orphan drugs with multiple indications to be developed, over 16.7 million LYs would be lost over the next 15 years	10
Conclusion	10
Appendices	11

Introduction

Orphan drugs are developed to treat rare diseases, defined as conditions affecting fewer than 200,000 people, such as genetically-linked cancers, cystic fibrosis, amyotrophic lateral sclerosis (ALS) and severe pediatric disorders like Gaucher disease and spinal muscular atrophy. While each rare disease affects a relatively small number of individuals, there are an estimated 7,000 known rare diseases collectively impacting about 1 in 10 Americans.¹ Notably, more than half of those affected by rare diseases are children. Approximately 95% of rare diseases still lack an FDA-approved, disease-specific treatment, leaving a significant and ongoing unmet need for patients and their families.²

The passage of the Orphan Drug Act (ODA) in 1983 marked a turning point in the treatment of these conditions, spurring innovation and investment in areas that were previously overlooked due to limited incentives.³ Prior to the passage of the ODA, only 38 orphan products had been approved by the Food and Drug Administration (FDA). Since then, however, that number has grown dramatically, with more than 650 medicines now indicated for patients with rare diseases.⁴

This surge in orphan drug development has significantly improved the lives of patients with rare and often life-threatening conditions by offering effective treatments where none previously existed. These therapies have enabled better disease management, enhanced quality of life, and, in many cases, prolonged survival. By addressing the unique needs of underserved communities, orphan drugs represent a critical advancement in personalized and equitable healthcare. For instance, Trikafta (elexacaftor/ivacaftor/tezacaftor) has dramatically improved lung function,⁵ reduced hospitalizations,⁶ and extended life expectancy for individuals with cystic fibrosis.⁷ Similarly, drugs like Exondys 51 (eteplirsen), Viltepso (viltolarsen), and Elevidys (delandistrogene moxeparvovec) have offered new hope for patients with Duchenne muscular dystrophy, a progressive condition that previously had no disease-modifying treatments.⁸ These breakthroughs underscore how targeted incentives can spur innovation that directly improves lives.

The 2022 Inflation Reduction Act (IRA) introduced the Medicare Drug Price Negotiation Program (MDPNP), aimed at reducing healthcare costs. One critical aspect of the IRA is its “sole orphan exclusion,” which excludes orphan drugs treating a single rare disease from MDPNP eligibility. This means that a drug is excluded from MDPNP only if it has received FDA approval for a single orphan indication but no additional designations or non-orphan approvals. However, if the manufacturer seeks an additional orphan

drug designation, the drug loses its sole orphan exclusion and becomes eligible for negotiation, regardless of whether the second indication ultimately receives FDA approval. This disincentivizes not only the development of new indications for existing orphan drugs—since pursuing other uses would make the drug negotiation eligible—but also may make the development of orphan drugs less financially attractive if only one indication is typically pursued. This distinction has major implications for pharmaceutical innovation and strategy. For example, Empliciti (elotuzumab), approved solely for multiple myeloma, a rare blood cancer, would be excluded from price negotiation. In contrast, Cotellic (cobimetinib), is approved for two distinct rare cancers: unresectable melanoma (skin cancer) with a BRAF V600E or V600K mutation and histiocytic neoplasms, which is another type of rare of blood cancer. Cotellic’s multi-indication status excludes it from the sole orphan exclusion status despite its substantial survival benefits across these rare diseases. This illustrates how the IRA’s pricing reforms could influence some of the most clinically impactful orphan drugs. As a result, this policy raises concerns about how to balance cost control with the need to support innovation for rare disease that often have significant unmet need.² The significant benefit of new treatments for rare diseases is often overlooked in these discussions. Limiting price negotiation exceptions to sole orphan drugs may discourage developers from pursuing additional rare or non-rare indications, potentially slowing future innovation and restricting patient access to life-changing therapies.⁹

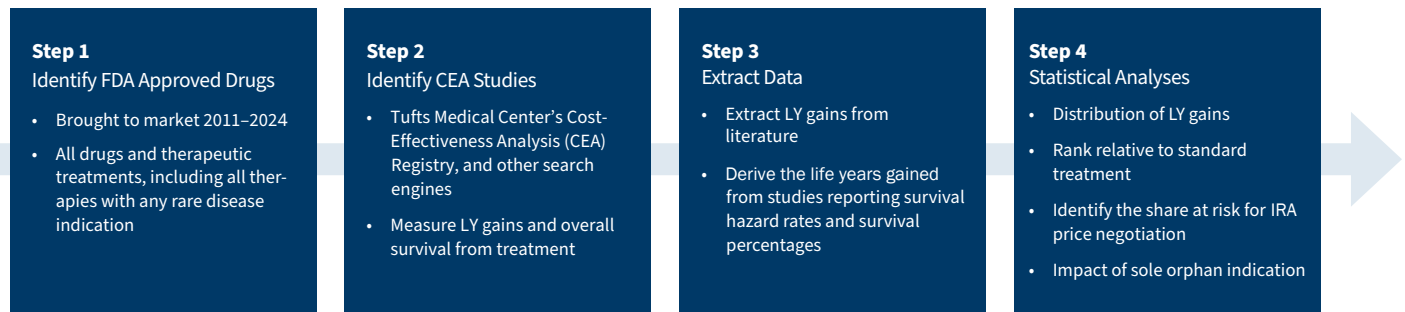
To address these concerns and better understand the impact of the IRA’s sole orphan exclusion, this study examines the relative value of orphan drugs compared to non-orphan drugs in terms of health benefits, specifically life years (LY) gained. Additionally, we assess the potential health benefits at risk due to the sole orphan exclusion by modeling scenarios where drug development for multiple rare disease indications might be discouraged.

The specific research questions answered in this paper are the following:

1. Do orphan drugs provide more health benefits per patient than non-orphan drugs?
2. Do follow-on indications for orphan drugs offer more health benefits per patient than non-orphan drugs?
3. What share of orphan drugs are at risk of IRA drug price negotiation?
4. What is the potential health impact of the sole orphan exclusion on the health of patients with rare disease?

Methodology

Figure 1: Methodology Implemented



Step 1: Identify all FDA Approved Drugs

First, we identified all drugs and therapeutic treatments brought to market between 2011–2024. These treatments were identified using the FDA Center for Drug Evaluation and Research novel drug approval website. From each FDA label, we identified the treatment's approval date, indications, and whether it has any rare disease indications. The FDA classifies drugs as orphan if any of their indications are orphan. However, throughout this analysis we define orphan status as is relevant for the IRA sole exclusion, so a drug is classified as IRA Orphan if its first indication is orphan. For example, Stivarga (regorafenib) and Horizant (gabapentin enacarbil) are technically classified as orphan by the FDA but since their first indications are not orphan, they are not classified as orphan in this analysis. (See Appendix for the full list of rules applied in the analysis.)

Step 2: Identify CEA Studies

Second, we identified cost-effectiveness analysis (CEA) models that measured the LY gains for each treatment. We used the Tufts Medical Center's CEA Registry,¹⁰ Google Scholar, PubMed, and other relevant sources to find CEAs. CEA studies were selected based on a criteria that prioritizes quantified health benefits from the treatment's indication. If no CEA reporting on LY gains were found, we searched for LY gains in the clinical trial results reported on the drug label. (See Appendix for full criteria for CEA study selection.)

Step 3: Extract Data

Third, we extracted CEA information for the first indication approved for all the drugs. For orphan drugs, we also extracted CEA survival gains for all follow-on orphan indications and the first approved non-rare indication, as well, if the treatment has both rare and non-rare conditions.

Step 4: Statistical Analysis

Next, based on the extracted LY gains, we performed statistical tests to see if rare disease health gains are statistically larger than those of other treatments.

Additionally, we calculated the share of orphan drugs are at risk of IRA drug price negotiation. Currently 26% orphan drugs in our database have more than one indication. Since these drugs are all relatively recently approved, it is likely that many of them will acquire more indications eventually. In order to estimate a more accurate share of orphan drugs at risk for IRA price negotiation, we extrapolated from our database the future likely number of indications. To do this, we calculated the likelihood of an additional indication for each orphan drug based on the number of years since approval. The distribution was based on a constant hazard ratio using the number of years between the first and second indications among those with multiple indications.

Lastly, we modelled various scenarios to identify the health benefits at risk due to the sole orphan exclusion and calculated these at-risk benefits. To quantify the life-years (LYs) at risk under each scenario, we multiplied the survival gain per person (relative to standard treatment) by the disease's annual incidence, market uptake (assumed to be 100%), and the total U.S. population in 2024. For orphan drugs lacking published survival gain estimates, we applied the average life-year gain from those with available data. See appendix for the detailed methodology used to calculate these survival gains at risk.

Descriptions of Orphan and Non-Orphan drugs included in this analysis

We distinguish between orphan and non-orphan drugs based on their first approved indication. If the first approved indication is classified as a rare condition then the drug is classified as orphan. If the first approved indication is not a rare condition then the drug is classified as non-orphan, even if later approved (follow-on) indications are rare. The orphan drugs are then divided into 3 orphan drug categories based on their indications. Table 1 shows the different categories of drugs, the composition of the 602 approved drugs in our database and provides some example drugs for each category.

Limitations

This analysis has a few limitations. First, this analysis relies on LYs as the primary outcome measure to assess clinical benefit, assuming they capture the full variation in treatment value. While LYs reflect patient longevity, they do not reflect changes in patients' quality of life—such as reduced disability, or improved daily functioning, nor do they account for broader social or economic outcomes that also influence value. Second, we evaluate only the first indication per non-rare disease treatment, which may lead to over or underestimation of health benefits if follow-on indications differ in efficacy. This methodological choice was chosen

for feasibility purposes, as even with this limitation, we still include over 100 non-orphan drugs in our analysis. Third, each treatment is represented by a single cost-effectiveness analysis (CEA) model, potentially omitting additional data that could more fully represent its benefits. Fourth, translating CEA model results to real-world outcomes poses challenges, as models are based on efficacy data, which may not align with real-world effectiveness. Additionally, there may be publication bias in the available CEA literature, as studies may be more likely to be published for treatments that appear more cost-effective, or for high-cost therapies that attract greater interest from researchers, payers, and other stakeholders. However, it is not clear if this publication bias would have a larger impact on orphan compared to non-orphan drugs, so the net directional impact of any publication bias is unclear.

Lastly, there are some limitations with respect to our extrapolation. Our analysis relies on assumptions about future indication expansion, which may not materialize as projected. Prevalence data were incomplete for many rare diseases—more than 60% lacked reliable prevalence estimates—requiring imputation based on available data. Furthermore, our projections extend over a 15-year time horizon, introducing additional uncertainty given the evolving landscape of rare disease treatment and policy.

Table 1: Composition of Drugs

	Brief Definition	Sample Size	% of Database	Example Drugs
Orphan vs Non-Orphan				
Orphan Drugs	Drugs whose first indication is a rare condition	291	48%	Tagrisso (osimertinib), Ultomiris (ravulizumab)
Non-Orphan Drugs	Drugs whose first indication is not a rare condition	311	52%	Trulicity (dulaglutide), Ozempic (semaglutide)
Types of Orphan Drugs				
Single Orphans	Orphan Drugs with a Single indication	231	38%	Biktarvy (bictegravir, embitcitabine, tenofovir alafenamide), Strensiq (asfotase alfa)
Multi-Rare Orphans	Orphan Drugs with Multiple Rare Indications	44	7%	Imbruvica (ibrutinib), Calquence (acalabrutinib)
Multi Non-Rare Orphans	Orphan Drugs with any Non-Rare Indications	16	3%	Cholbam (cholic acid), Tafinlar (dabrafenib)

Findings

Finding #1: Orphan drugs impact on patient survival is more than 4 times larger than the survival gains of non-orphan drugs

Orphan drugs provide an average of 2.61 LYs gained for their first approved indication, compared to 0.63 LYs for non-orphan drugs—representing a 4.1-fold greater benefit ($p < 0.001$). See Figure 2.

While health gains are ‘right skewed’, with the median LY gains lower than the average LY gains—we still observe that median life year gains for orphan drugs are more than 4 times higher than those of non-orphan drugs. Specifically, Breyanzi (lisocabtagene maraleucel) and Pomalyst (pomalidomide) are orphan drugs with the typical (i.e., median) survival gain of 1.2 LY gains per person; in contrast, Fycompa (perampanel) and Tecentriq (atezolizumab)—the typical (i.e., median) non-orphan drugs—have LY gains of 0.26 and 0.28 per person, respectively. Survival gains for the most effective orphan drugs are also much higher than for the most effective non-orphan drugs. The top 3 orphan drugs in terms of survival gains are Strensiq (asfotase alfa), Lenmeldy (atidarsagene autotemcel) and Brineura (cerliponase alfa), which have 21.96, 18.22 and 17.63 additional LYs gained, respectively. These figures are significantly higher than the corresponding top 3 non-orphan drugs—Keytruda (pembrolizumab), Ozempic (semaglutide) and Libtayo (cemiplimab-rwlc)—with LY gains of 10.07, 4.71 and 4.65 respectively. In fact, Keytruda (pembrolizumab) itself was initially approved as an orphan drug, but in our classification algorithm—

whereby drugs with more than 5 non-orphan indications are considered non-orphan—we classified the treatment as non-orphan for the purposes of this analysis.

In short, orphan drugs dominate across all statistical metrics examined: mean, median and max.

While Figure 2 examines the health gains for the first indication only, we also examined whether this significant LY gain difference holds up across all approved indications for orphan drugs. When considering all approved indications for orphan drugs against the first indication for non-orphan drugs, orphan drugs still demonstrate a significantly higher impact, providing 3.7 times more LY gains ($p < 0.001$). Additionally, when analyzing only their orphan indications, orphan drugs provide 3.8 times as many LY gains than non-orphan drugs ($p < 0.001$). See Appendix Table 1. Hence, regardless of the indications, orphan drugs increase the survival gains significantly more than non-orphan drugs.

Finding #2: Orphan drugs with multiple rare disease indications provide more than 3 times the survival gains as non-orphan drugs

The development of new indications for existing drugs has found to be much less costly than the development of de novo drugs.¹¹ Thus, use of existing drugs—whether orphan or not—to treat new diseases can save cost and reduce time to market compared to having to develop de novo therapies. Nevertheless, the sole orphan exclusion explicitly aims to distinguish sole orphan drugs from orphan drugs with multiple indications.

Several orphan drugs have later acquired approval for additional rare disease indications that offer health benefits equal to or greater than their original approved indication. For instance, the original indication for Brukinsa (zanubrutinib) was mantle cell lymphoma (MCL) for which it provides gains of 0.98 LYs, but later Waldenström’s macroglobulinemia (WM) was added as another indication for which it provides gains of 0.94 LYs.^{12; 13} A sensible question to ask then, is whether multi-rare orphan drugs still provide significantly more health benefits than non-orphan drugs. While the number of such multi-rare orphan drugs is relatively small, they are precisely the subset that would be affected by policies like the Orphan Cures Act—suggesting that, although few in number, their health impact may be substantial.

Multi-rare orphans provide significantly more health gains than non-orphan drugs: 3.3 times the survival gain (2.06 LY gained vs. 0.63 LY gained for non-orphan, $p = 0.003$). (Figure 3 and Appendix Table 1).

Figure 2: First Indication LY Gains for Orphan Drugs and Non-Orphan Drugs

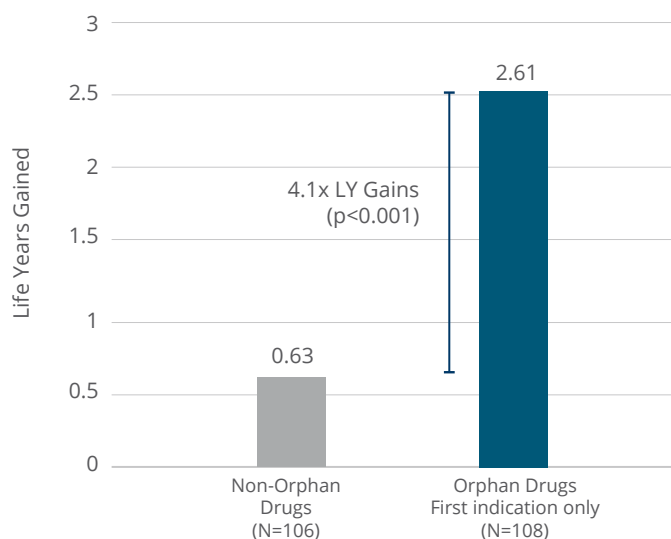
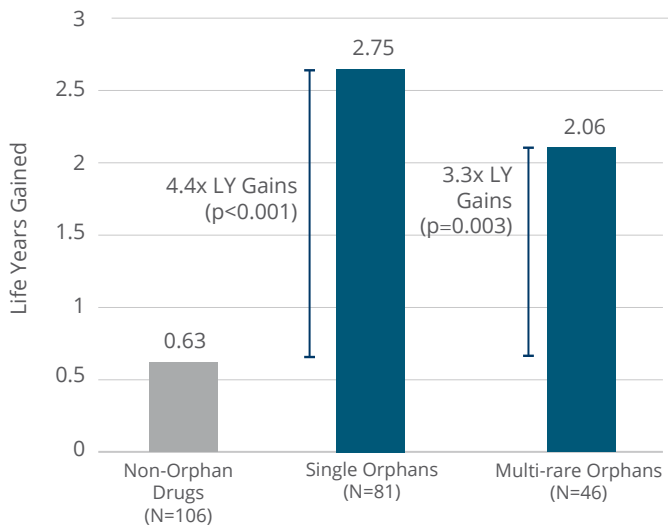


Figure 3: LY Gains for Single Orphans and Multi-Rare Orphans versus Non-Orphan Drugs

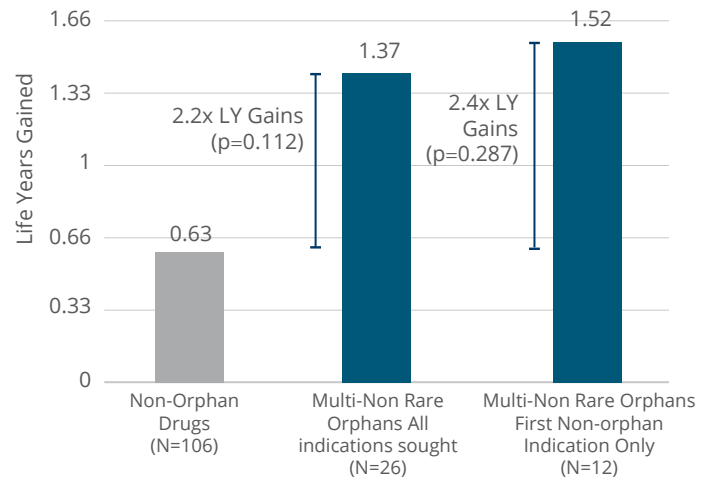


Policymakers and analysts have critiqued the use of orphan drug status as a strategy to secure market exclusivity and higher prices, particularly when drugs approved for rare diseases later expand to broader indications.^{14; 15} A sensible question policymakers may ask would be whether orphan drugs' with any non-orphan indications provide similar health benefits as de novo non-orphan drugs.

Multi non-rare orphans provide survival gains that are 2.2 times as high as non-orphan drugs (1.37 LY vs. 0.63 for non-orphans, $p=0.112$). However, these gains are still lower than those provided by single orphans and multi-rare orphans. When focusing on only the first non-orphan indication of the multi non-rare orphans we found an average LY gain of 2.4 times that of non-orphan (average of 1.52 LY gains vs. 0.63 LY gains, $p=0.287$). While there is no statistically significant difference—likely due to the relatively small sample sizes examined—multi non-rare orphan drugs provide numerically superior survival gains compared to non-orphan drugs (Figure 4 and Appendix Table 1).

Some examples of multi non-rare orphans that provide noteworthy LY gains on their non-rare indications are Lynparza (olaparib) which provides 1.5 LY gain per person on its non-rare indication of breast cancer and Repatha (evolocumab) which provides 2.3 LY gains on its non-rare indication of primary hyperlipidemia.^{16; 17}

Figure 4: LY Gains for Multi-Non Rare Orphans versus Non-Orphan Drugs



Finding #3: Because many orphan drugs treat multiple rare and non-rare diseases, 58% of orphan drugs could be eligible for Medicare Drug Price Negotiation

Many policymakers may wonder what share of orphan drugs will eventually have multiple indications. In our current database, 26% of orphan drugs have a single indication, but this is a clear underestimate as many of the treatments were recently approved and these drugs may add indications over time. Sahragardjoonegani, et al. (2021) explored the frequency and timing of add on indications across all new small-molecule drugs FDA approved between July 1997 and May 2020.¹⁸ They found that 11.4% have more than one indication at approval or within the first two years, 7.6% get another indication during their third or fourth year, and 17.4% in year 5 and after.

When we consider the likely future number of indications based on historical precedent in our database, we found that 58.2% of all approved orphan drugs would likely have multiple indications and thus be susceptible for IRA price negotiation. We conducted sensitivity analyses based on likelihood of next indication estimates provided in the literature and found similar results (see Appendix Table 2).¹⁸

Finding #4: If the sole orphan exclusion prevented all orphan drugs with multiple indications to be developed, over 16.7 million LYs would be lost over the next 15 years

We found that orphan drugs provide an average of 2.61 LYs gained on their first approved indication. Now let us imagine a world where no orphan drugs with multiple indications would be brought to the world. The average orphan condition has an incidence rate of 5.72 per 100,000.¹⁹ If 58% of them would not have been brought to market, then the LY impact would be 16,793,818 LYs. While this is likely an overestimate—it is not the case that 100% of orphan drugs with more than one indication would be removed from the market—it does show the health impacts of the sole orphan exclusion are large.

Conclusion

In summary, orphan drugs offer substantially greater survival benefits compared to non-orphan drugs, providing over four times the LY gains on their first approved indication. This advantage remains even when focusing specifically on drugs with multiple rare disease indications, which, on average, deliver three times the LY gains of non-orphan treatments and when focusing specifically non-orphan indications—though this difference between orphan and non-orphan drugs is not statistically significant. Looking ahead, we estimate that approximately 58% of drugs could be subject to price negotiation under the IRA, placing an estimated 16.7 million life-years at risk over the next 15 years. These findings underscore the importance of carefully evaluating the potential clinical trade-offs of future pricing and policy decisions, particularly for therapies targeting rare diseases.

Appendices

Rules Applied in the Analysis

1. Classify a drug as IRA Orphan if it's first indication is Orphan.
2. The number of indications is the number of bullets there are listed on the most recent FDA label unless there are indication specific headings, then the number is the number of headings.
3. Classify "pediatric cases only" orphan indications as non-orphan.
4. If all indications can be classified under the orphan approved designation, then consider it to be a Sole Orphan Drug (rather than an Orphan Drug with Multiple Orphan indications).
5. Do not include drugs that the FDA has approved and then later removed in the analysis.
6. Classify drugs with 5 or more non-orphan indications as non-orphan.
7. Remove drugs that are used solely for diagnostic purposes.
8. Remove Cord Blood Gene Therapies.
5. If no CEA studies were identified in the Tuft's registry for certain drugs, we searched for CEA studies through PubMed or Google Scholar to examine if an alternative publication was available for the first indication of that drug. We used the following search terms "drug/therapy name" + "cost effectiveness", "drug/therapy name" + "cost effectiveness analysis", or "drug/therapy name" + "cost-effectiveness" + "LY". In this search, applied the same criteria as the CEA search used by the Tuft's registry.
6. If life years gained data were not reported in a CEA study, a study that contained LY will be prioritized-even if the study was published farther from the FDA approval date.
7. If no LY can be identified in any CEA Study used, LY reported from the clinical trial section of the FDA label was used. Some clinical trials may not provide data on life years but may provide a survival hazard rate or share of patients that survive a given time period. For labels that reported OS as a percent (i.e., percent survival after 5 years), we derived the median survival in years using the following formulas.

$$OS_r = 1 - S_t^{\frac{1}{t}}$$

$$OS_y = \frac{\ln(.5)}{\ln(OS_r)}$$

where OS_r is the overall survival risk rate, S_t is the overall survival percentage at time t (i.e., 1 year, 5 years, etc.), and OS_y is the overall survival in years.

CEA Study Criteria

1. Incremental LYs were primarily collected from CEA studies identified using the Tufts Medical Center's Cost-Effectiveness Analysis (CEA) Registry. CEA studies that were produced more than 1 year before the FDA approval year were excluded.
2. If multiple CEA studies were identified within the Tuft's registry, the study closest to the approval date that had the first indication (as stated in the FDA label) was selected. If a study was found to be published farther away from the FDA approval date, but contained health benefits data on the first indication, that study was selected over other published CEA studies that contained information on secondary indications.
3. If a later study reported health benefits from a population that was an earlier line of therapy, that study was selected instead of an earlier study. Studies that estimate the drug's health benefits in monotherapy were prioritized over other prior studies as well.
4. If a study did not contain life years gained or overall survival metrics in the paper or from cited clinical trial papers, a CEA study published later that contained this information was used.

8. If no OS was identified in the FDA label, health benefits data for those treatments were coded as missing.

Methodology Used to Calculate Survival Gains At Risk

$$E(\text{Survival gain at risk})_i = \sum_t \left(\frac{\text{Survival gain}}{\text{person}} \right)_i (\text{Disease incidence } \%)_i (\text{US population}) (\text{Market uptake } \%)$$

Where i is the rare disease of interest, t is the time period in year, $\left(\frac{\text{Survival gain}}{\text{person}} \right)_i$ is the overall survival gain from orphan treatments in comparison to the standard treatments for rare condition i in the scenario, $(\text{Disease incidence } \%)_i$ is the incidence of the rare condition i ,¹⁹ and $(\text{Market uptake } \%)$ is the percentage of people with the condition who are treated for the rare disease (which we assumed to be 100%). We used the US population at the end of the year 2024, which was 341,140,964.²⁰ For Orphan drugs with no LY results available we used the average LY gain among those with estimates.

Appendix Table 1: LY Gains Summary Table

Level	Which Indications	Number of Drugs	# of Indications with LY gain estimates	Average LY gained	Difference	Ratio of Orphan to Non-Orphan Gains	p-Value for Difference = 0
Non-Orphan Drugs	First Only	311	106	0.63	-	-	-
All Orphan Drugs	First Only	291	108	2.61	1.98	4.15	<0.001
Single Orphans	All Sought	251	81	2.75	2.13	4.39	<0.001
Multi-Rare Orphans	All Sought	44	46	2.06	1.43	3.28	0.003
Multi-Non-Rare Orphans	All Sought	16	26	1.97	0.76	2.19	0.112
Multi-Non-Rare Orphans	First Non-Orphan Only	16	12	1.52	0.9	2.4	0.287
All Orphan Drugs	Only Orphan	291	161	2.98	1.75	3.79	<0.001
All Orphan Drugs	All Sought	291	153	2.31	1.68	3.68	<0.001

Appendix Table 2: Sensitivity Analysis on Survival Gains at risk for and Impact of the IRA Price Negotiation

		Total LYs at Risk	
	Percent of Drugs at Risk	Over 15 years	Over 30 years
Method 1: Identifies the share of orphan drugs at risk for IRA price negotiation, based on the current observed number of indications.			
	25.8%	7,502,393	15,004,786
Method 2: Identifies the share of orphan drugs at risk based on extrapolation from our database on the future likely number of indications (constant hazard).			
	58.2%	16,793,818	33,587,636
Method 3: Identifies the share of orphan drugs at risk based on extrapolation from more generalizable estimates in the literature.			
	64.5%	18,611,706	37,223,412

References

1. Wan EL, E. Y., Gao W, Yoon R. (2023). Zebras Among Us: Advocating for the 30 Million Americans Living with Rare Disease. Med Sci Educ. <https://pmc.ncbi.nlm.nih.gov/articles/PMC10597899/>
2. Delivering Hope for Rare Diseases. (2023). National Institutes of Health. Retrieved 06/05/2024 from https://ncats.nih.gov/sites/default/files/NCATS_RareDiseasesFactSheet.pdf
3. Fermaglich LJ, M. K. (2023). A comprehensive study of the rare diseases and conditions targeted by orphan drug designations and approvals over the forty years of the Orphan Drug Act. Orphanet Journal of Rare Diseases. <https://ojrd.biomedcentral.com/articles/10.1186/s13023-023-02790-7>
4. Building on 40 Years of the Orphan Drug Act. (2022). Rare Disease Company Coalition. <https://www.rarecoalition.com/wp-content/uploads/ODA-Overview.pdf>
5. Lee T, S. G., Altenburg J, Millar SJ, Geiger JM, Jennings MT, Lou Y, McGarry LJ, Van Brunt K, Linnemann RW. (2023). EFFECT OF ELEXACAFOR/TEZACAFOR/IVACAFOR ON ANNUAL RATE OF LUNG FUNCTION DECLINE IN PEOPLE WITH CYSTIC FIBROSIS. J Cyst Fibros. <https://pubmed.ncbi.nlm.nih.gov/36581485/>
6. Marshall, L. Z., Espinosa, R., Starner, C. I., & Gleason, P. P. (2023). Real-world outcomes and direct care cost before and after elexacaftor/tezacaftor/ivacaftor initiation in commercially insured members with cystic fibrosis. Journal of Managed Care & Specialty Pharmacy, 29(6), 599-606. <https://doi.org/10.18553/jmcp.2023.29.6.599>
7. Lopez A, D. C., Hernandez GV, MacGregor G, Rubin JL. (2023). Elexacaftor/tezacaftor/ivacaftor projected survival and long-term health outcomes in people with cystic fibrosis homozygous for F508del. Journal of Cystic Fibrosis, Volume 22, Issue 4. https://www.sciencedirect.com/science/article/pii/S1569199323000486?utm_source=chatgpt.com
8. Aartsma-Rus A, K. A. (2017). FDA Approves Eteplirsen for Duchenne Muscular Dystrophy: The Next Chapter in the Eteplirsen Saga. Nucleic Acid Ther. <https://pmc.ncbi.nlm.nih.gov/articles/PMC5312460/>
9. Vogel M, Z. O., Feldman WB, Chandra A, Kesselheim AS, Rome BN. (2024). Cost of Exempting Sole Orphan Drugs From Medicare Negotiation. JAMA Internal Medicine, 184(181): 163-169.
10. Cost-Effectiveness Analysis (CEA) Registry. <https://cevr.tuftsmedicalcenter.org/databases/cea-registry>
11. Pinzi L, B. N., Rastelli G. (2024). How drug repurposing can advance drug discovery: challenges and opportunities. Front. Drug Discov. <https://www.frontiersin.org/journals/drug-discovery/articles/10.3389/fddsv.2024.1460100/full>
12. Neda Alrawashdh, A. M., Marion Slack, and Ivo Abraham. (2020). Economic Evaluation of Ibrutinib Versus Acalabrutinib Versus Zanubrutinib for Patients with Relapsed or Refractory Mantle Cell Lymphoma 62nd ASH Annual Meeting and Exposition. <https://ash.confex.com/ash/2020/webprogram/Paper136358.html>
13. Jorge J. Castillo, K. Y., Rongzhe Liu, Yu Wang, Aileen Cohen, Todd M. Zimmerman, Qian Zhao, Gijs van de Wetering, Xin Gao, and Boxiong Tang. (2021). Cost-effectiveness of zanubrutinib versus ibrutinib in adult patients with Waldenström macroglobulinemia in the United States. ASCO Annual Meeting. https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.e18856
14. Saganowsky, E. (2016). Orphan drugs used in wider settings come with sizable price hikes, report finds. Fierce Pharma. <https://www.fiercepharma.com/pharma/orphan-drugs-used-wider-settings-come-sizable-price-hikes-report-finds>
15. Joszt, L. (2019). Orphan Drugs Are Driving Skyrocketing Drug Costs, AHIP Finds. American Journal of Managed Care. https://www.ajmc.com/view/orphan-drugs-are-driving-skyrocketing-drug-costs-ahip-finds?utm_source=chatgpt.com
16. Polyzoï M, E. M., Reithmeier A, Jacob J, Karlsson E, Bertranou E, Linderholm B, Hettle R. (2023). Cost-Effectiveness Analysis of Adjuvant Olaparib Versus Watch and Wait in the Treatment of Germline BRCA1/2-Mutated, High-Risk, HER2-Negative Early Breast Cancer in Sweden. Pharmacoecon Open. <https://pmc.ncbi.nlm.nih.gov/articles/PMC10884392/>
17. Gandra SR, V. G., Fonarow GC, Lothgren M, Lindgren P, Somaratne R, van Hout B. (2016). Cost-Effectiveness of LDL-C Lowering With Evolocumab in Patients With High Cardiovascular Risk in the United States. Clin Cardiol. <https://pmc.ncbi.nlm.nih.gov/articles/PMC5074319/>
18. Sahragardjoonegani B, B. R., Kesselheim AS, Hollis A. (2021). Repurposing existing drugs for new uses: a cohort study of the frequency of FDA-granted new indication exclusivities since 1997. Journal of Pharmaceutical Policy and Practice, 1-8. <https://pmc.ncbi.nlm.nih.gov/articles/PMC7780607/>
19. Prevalence and incidence of rare diseases: Bibliographic data. (2024). https://www.orpha.net/pdfs/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf
20. U.S. and World Population Clock. Retrieved 05/30/2025 from <https://www.census.gov/popclock/>

JASON SHAFRIN

Senior Managing Director
(213)-452-6483
jason.shafirin@fticonsulting.com

MARIE STEELE-ADJOGNON

Senior Director
(667)-321-7804
marie.steele-adjognon@fticonsulting.com

Funding for this research was provided by Alexion and AstraZeneca. The views and opinions presented herein are solely those of the authors and the Center and do not necessarily reflect the views of FTI Consulting, Inc., its management, its subsidiaries, its affiliates, its other professionals, or other organizations with which the authors are or have been affiliated. FTI Consulting, Inc., including its subsidiaries and affiliates, is a consulting firm and is not a certified public accounting firm or a law firm.

FTI Consulting is an independent global business advisory firm dedicated to helping organizations manage change, mitigate risk and resolve disputes: financial, legal, operational, political & regulatory, reputational and transactional. FTI Consulting professionals, located in all major business centers throughout the world, work closely with clients to anticipate, illuminate and overcome complex business challenges and opportunities. © 2025 FTI Consulting, Inc. All rights reserved. fticonsulting.com