Biosimilars in the United States: Market Dynamics and Patient Out-of-Pocket Costs

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Abstract

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Background

The United States biosimilars market is growing rapidly and has led to significant savings for the health care system and payers. However, market complexities, barriers to entry, and fewer biosimilars in the pipeline than expected has led to concerns about the long-term sustainability of the biosimilars market and therefore threatened savings. We characterized eight physician-administered biologics markets in terms of price declines and reference product market share to better understand the heterogeneity between these markets. We also estimated the effect of biosimilar competition on patient out-of-pocket costs for rheumatology biologics, to understand whether biosimilar competition is truly resulting in savings for patients.

Methods

For Aim 1, quarterly average sales price (ASP) data from the Centers for Medicare and Medicaid Services (CMS) Drug Pricing Files along with volume data from the standard Medicare Limited

Data Set (5% sample) for Medicare and the Merative™ MarketScan® Commercial Database for the commercial population were used as data sources, using price and volume (number of claims) for the following biologics: filgrastim, rituximab, infliximab, trastuzumab, pegfilgrastim, epoetin alfa, bevacizumab, and ranibizumab. We first characterized the markets descriptively, then used linear regression to assess the relationship between reference product market share and each biosimilar entry and to study biosimilar versus reference product price decline over time since biosimilar entry.

For Aim 2, the Merative™ MarketScan® Commercial Database was used to conduct an analysis of patient OOP costs before and after biosimilar competition using the methodology described by Callaway & Sant'Anna. We included infliximab, rituximab, and adalimumab as the drug groups of interest, as they are the rheumatology biologics with biosimilars available. The exposure was biosimilar competition and the outcome was biologic-related OOP costs.

Results

In Medicare, reference product market share declined consistently, though to varying degrees across molecule groups. In the commercial sector, market share trends were more variable, with some reference product markets remaining stable and others declining steeply. Price trends also differed substantially between payer sectors. In Medicare, biosimilars showed an 18.6% ($p<0.01$) greater price decline on average than reference products, while in commercial markets the overall result was not significant. Price decline patterns varied widely between the different biologics.

For patient out-of-pocket costs, we observed statistically significant savings due to biosimilar competition, with an average savings of over $1,000 in the infliximab and rituximab groups over the study period. When assessing treatment effect by duration of exposure, we observed increasing

savings over time, the longer biosimilars were available. In the adalimumab group, there was an increase in patient OOP costs in the year prior to biosimilar availability, which may reflect anticipatory price increases on the part of the reference manufacturer. There was minimal savings in the adalimumab group upon biosimilar entry, and no savings when accounting for one year of anticipation.

Conclusion

The first study provides evidence of the differences between biologic markets in both market share and price decline trends, and the challenge of generalizing predictions or drawing generalizable conclusions about biosimilar market behavior. The second study indicates that the availability of infliximab and rituximab biosimilars led to significant savings for patients in addition to the health care system as a whole, with more savings the longer biosimilars are on the market. Together, these studies highlight the importance of policies that incentivize development of biosimilars and support the long-term availability of biosimilars to preserve and increase savings for patients.

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INTRODUCTION

The United States biologics market is growing rapidly, representing close to half of drug spending.[1,2] Biosimilars obtain FDA approval on the basis of having no clinically meaningful differences from their reference product through a rigorous approval process.

The biosimilars market in the US is highly complex. High production costs, interchangeability regulations, payer policies, regulatory approval requirements, and other barriers can result in varied uptake of biosimilars, slower time to market, and fewer competitors.[3,4] These dynamics raise concerns about the long-term sustainability of the biosimilars market.[3,5] The current biosimilars market is highly concentrated in oncology and immunology therapeutics despite anticipated biologic patent expirations in many other areas, targeting reference products with more than $1.0 billion in annual sales.[1,5,6] Of 118 biologics expected to lose patent exclusivity in the next ten years, only twelve molecules have biosimilars in development.[5] This leads to concerns that biosimilar manufacturers may be hesitant to invest in biosimilar development and enter the market, which may lead to fewer biosimilars in the future. It is important for manufacturers to have more certainty about market behaviors to be able to justify biosimilar development to continue the benefits that biosimilar competition has provided thus far, such as improved access for patients and savings to the health care system.

Evidence shows that biosimilar competition can result in significant drug expenditure savings, but if the long-term sustainability of the biosimilars market is in question, these savings may be threatened.[2,5] The mechanism behind the savings is twofold: 1) the biosimilars typically enter at lower prices[5,7], so there can be direct savings from utilization of a lower-priced product, and 2) the presence of competition leads to overall prices coming down for the whole group – both reference

products and biosimilars. Studies to this point have typically focused on the former mechanism, to understand the direct savings due to biosimilar prices being lower. Very few have sought to understand the true effect of competition on overall prices.

Additionally, while the savings to the health care system and payers has been well documented, the evidence on whether biosimilar competition reduces patient out-of-pocket (OOP) costs remains mixed, especially in the commercial population.[8–11] Additionally, these studies generally compare biosimilar-related OOP costs to reference product-related OOP, which does not account for what would have happened to reference product prices in the absence of biosimilar competition (counterfactual price trends). Because reference product prices typically decline after biosimilars enter the market, these comparisons can demonstrate biosimilar savings relative to the reference product but cannot establish whether biosimilar competition itself led to lower overall OOP costs across the full biologic group (both biosimilars and reference products).

The objective of this dissertation was to help characterize the biosimilar markets of eight physician-administered biologics and to understand the impact of biosimilar competition on patient out-of-pocket costs in rheumatology biologics. First, we evaluated the rate of price decline in biosimilars compared to their reference products as well as the relationship between biosimilar competition (number of competitors) and reference product market share using fixed-effects linear regression, to understand how these markets are behaving in the Medicare and commercial sectors. Second, we assessed the effect of biosimilar competition on patient out-of-pocket costs for rheumatology biologics infliximab, rituximab, and adalimumab using a difference-in-differences (DID) analysis with comparable biologics without biosimilar competition as a control group.

The results of these studies will provide further evidence of the impact of biosimilar competition and will highlight the importance of policies that incentivize development of biosimilars to support

their long-term availability to preserve and increase savings and access for patients and the health care system.

CHAPTER 1. BIOSIMILAR MARKET DYNAMICS: PRICE AND VOLUME TRENDS

Chapter 1a. Price and Volume Trends Before and After Biosimilar Competition

Abstract

The US biologics market in the is growing rapidly and there is a large potential for the availability of biosimilars to increase savings for payers and patients. Several factors contribute to biosimilar markets differing substantially in market share and pricing trends. We examined price and market share dynamics in eight biologic markets in both Medicare and commercial populations, and found that while some markets behave similarly, most are very different from one another with respect to reference product market share over time and how quickly prices decline (or don't). These differences create uncertainty for manufacturers, which may contribute to decisions to avoid the market or for existing manufacturers to exit. Our findings highlight a need for addressing barriers to biosimilar competition from a policy perspective, in order to increase long-term savings.

Background

The United States biologics market is growing rapidly, representing close to half of drug spending.[1,2] Biosimilars, which obtain FDA approval on the basis of having no clinically meaningful differences from their reference product, typically enter the market at lower prices. Evidence shows that biosimilar competition can result in significant drug expenditure savings.[5,7]

Market complexities, including high production costs, interchangeability regulations, payer policies, regulatory approval requirements, and other barriers can result in varied uptake of biosimilars, slower time to market, and fewer competitors.[3,4] These dynamics raise concerns about

the long-term sustainability of the biosimilars market.[3,5] The current biosimilars market is highly concentrated in oncology and immunology therapeutics despite anticipated biologic patent expirations in many other areas, targeting reference products with more than $1.0 billion in annual sales.[1,5,6] Of 118 biologics expected to lose patent exclusivity in the next ten years, only twelve molecules have biosimilars in development.[5] There is concern that manufacturers may choose not to pursue biosimilar development, thus threatening the potential savings that biosimilars provide.

Thus, it is important to understand the unique biosimilar market dynamics to inform policy that will support competition and sustainability and therefore continued savings. We illustrate these points by assessing the dynamics of price and utilization of biosimilars and their reference products in eight therapeutic markets.

Methods

We examined quarterly price and market share in the Medicare and commercial health insurance populations from the time of initial biosimilar market entry in the first quarter of 2015 through the fourth quarter of 2023 (36 quarters). For Medicare, we used quarterly average sales price (ASP) data from the Centers for Medicare and Medicaid Services (CMS) Drug Pricing Files along with volume data from the standard Medicare Limited Data Set (5% sample) for the following biologics: filgrastim, rituximab, infliximab, trastuzumab, pegfilgrastim, epoetin alfa, bevacizumab, and ranibizumab.[12,13] The full list of products included and associated codes used to identify each product are in Appendix A, Section A1.

For the commercial insurance population, we used the CMS Drug Pricing Files crosswalk (HCPCS to NDC codes) for each quarter plus any additional NDC codes identified in Merative™ Micromedex® RED BOOK® Online to identify claims for the drugs of interest in the Merative™ MarketScan® Commercial Database.[12,14] We used gross payments to a provider ("PAY") as the

price, which is the amount eligible for payment under the medical plan terms (inclusive of patient cost-sharing) after applying rules such as discounts.

Gross payments and ASP were both adjusted for inflation to Q4 2024 using the Medical Care CPI.[15] Using the price and volume in each data source, we graphed each of the reference products and their biosimilars over our study period. We then descriptively compared the market dynamics in the eight biologic markets to each other and across the two payer types.

Results

Overall Results

A descriptive summary of the price and market share trends for each biologic market in the Medicare and commercial sectors is shown in Table 1-1.

Table 1-1. Summary of Price and Market Share Trends

	Price			***Market Share***	
Drug	***Commercial***	***Medicare***		***Commercial***	***Medicare***
Filgrastim	***Initial price:*** Biosims ≈ Ref ***Trend:*** Stable	***Initial price:*** Biosims < Ref ***Trend:*** Ref stable, Biosims ↓		***Ref:*** ↓ ***Biosims:*** ↑ (1st only)	***Ref:*** ↓ ***Biosims:*** ↑
Rituximab	***Initial price:*** Biosims < Ref ***Trend:*** All ↓, biosims more steeply	***Initial price:*** Biosims < Ref ***Trend:*** All ↓, biosims more steeply		***Ref:*** ↓ ***Biosims:*** ↑	***Ref:*** ↓ ***Biosims:*** ↑
Trastuzumab	***Initial price:*** Biosims < Ref ***Trend:*** All ↓, biosims more steeply	***Initial price:*** Biosims < Ref ***Trend:*** All ↓, biosims more steeply		***Ref:*** ↓ ***Biosims:*** ↑ (1st and 2nd only)	***Ref:*** ↓ ***Biosims:*** ↑
Infliximab	***Initial price:*** Biosims ≈ Ref ***Trend:*** All ↓	***Initial price:*** Biosims ≈ Ref ***Trend:*** All ↓		***Ref:*** ↓ ***Biosims:*** ↑ (1st only)	***Ref:*** ↘ ***Biosims:*** ↗
Pegfilgrastim	***Initial price:*** Biosims < Ref ***Trend:*** All ↓, biosims more steeply	***Initial price:*** Biosims ≈ Ref ***Trend:*** All ↓		***Ref:*** ↘ ***Biosims:*** ↗	***Ref:*** ↘ ***Biosims:*** ↗
Bevacizumab	***Initial price:*** Biosims < Ref ***Trend:*** All ↓, biosims more steeply	***Initial price:*** Biosims < Ref ***Trend:*** All ↓, biosims more steeply		***Ref:*** ↓ ***Biosims:*** ↑ (1st and 2nd only)	***Ref***: ↘ ***Biosims:*** ↗
Epoetin alfa	***Initial price:*** Biosims < Ref ***Trend:*** Unclear	***Initial price:*** Biosims ≈ Ref ***Trend:*** All ↓		***Ref:*** ↓ ***Biosims:*** ↑ (1st only)	***Ref:*** ↓ ***Biosims:*** ↑ (1st only)
Ranibizumab	***Initial price:*** Biosims < Ref ***Trend:*** All ↓, biosimilars more steeply	[Not enough data]		[Not enough data]	[Not enough data]

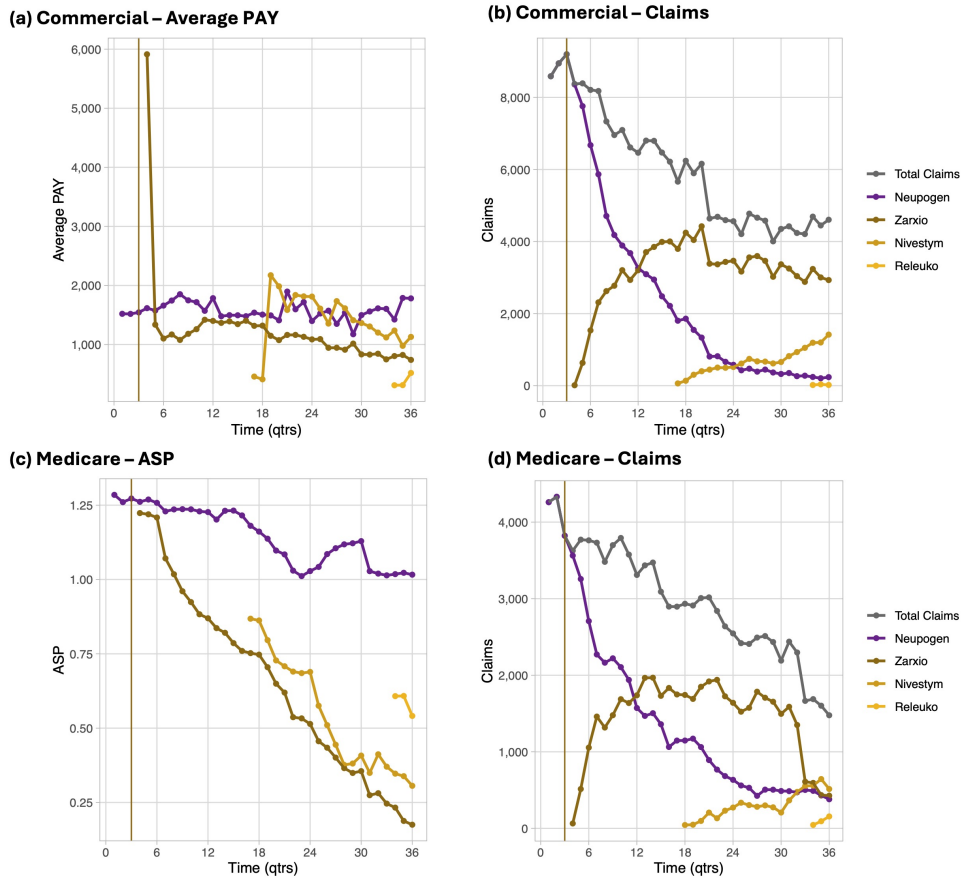
Key: Biosims – biosimilars; Ref – reference product; ≈ - approximate; < - less than; ↓ - substantial decrease; ↑ - substantial increase; ↘ - moderate/gradual decrease; ↗ - moderate/gradual increase

Filgrastim

Filgrastim (Figure 1-1) had the earliest biosimilar entry of those in our sample, with Zarxio® (filgrastim-sndz, first biosimilar approved under the BPCIA) entering the market in quarter 4 of 2015. In Medicare, the ASP of the branded product (Neupogen®) remained stable despite biosimilar entry while the two biosimilar ASPs declined substantially after entry. Zarxio® (first biosimilar to enter) was able to overtake Neupogen® in market share after about nine quarters on the market, while Nivestym® was slower to gain market share. There was a large drop in filgrastim claims (particularly Zarxio®) starting in 2023, which may be due to external factors such as a shift toward more cancer immunotherapies that do not require the use of filgrastim.

In the commercial sector, the average gross payment per claim was similar between all products and remained stable throughout the study period in contrast with the steep biosimilar ASP decline in Medicare. The market share decline was similar between the Medicare and commercial sectors.

Figure 1-1. Filgrastim Commercial and Medicare Markets, 2015-2023



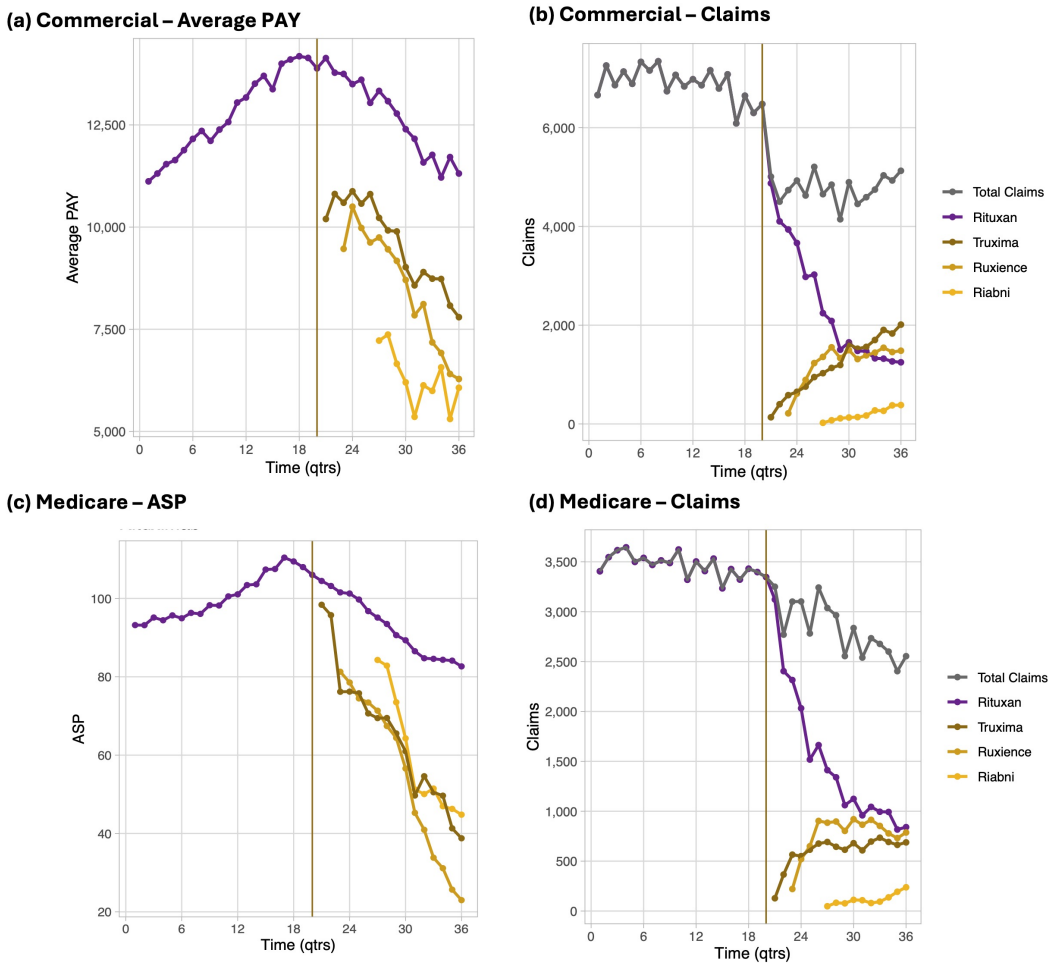
The vertical line on each graph indicates the quarter immediately prior to the first biosimilar entry. Biosimilar entry was defined as the first quarter in which a biosimilar product had both price (gross PAY for commercial, ASP for Medicare) and volume (claims) data available.

Rituximab

The rituximab markets (Figure 1-2) are an example of similar behavior between Medicare and commercial. In both datasets, the price of the reference product, Rituxan®, gradually increases leading up to the first biosimilar entry and then gradually declines. The biosimilars enter at lower prices and decline more steeply, in Medicare with biosimilars having declined to 39% of their entry prices (on average) versus the reference product only declining to 78% by the end of 2023. The decline was more comparable in commercial, with the biosimilars having declined to 76% of their entry prices (on average) versus the reference product declining to 81%.

Market share in both Medicare and commercial for rituximab also looks similar, with the reference product market share declining after biosimilar entry and both the first and second biosimilars both gaining substantial market share (Truxima® and Ruxience®, respectively). The third biosimilar, Riabni®, did not appear to gain substantial market share in either dataset.

Figure 1-2. Rituximab Commercial and Medicare Markets, 2015-2023



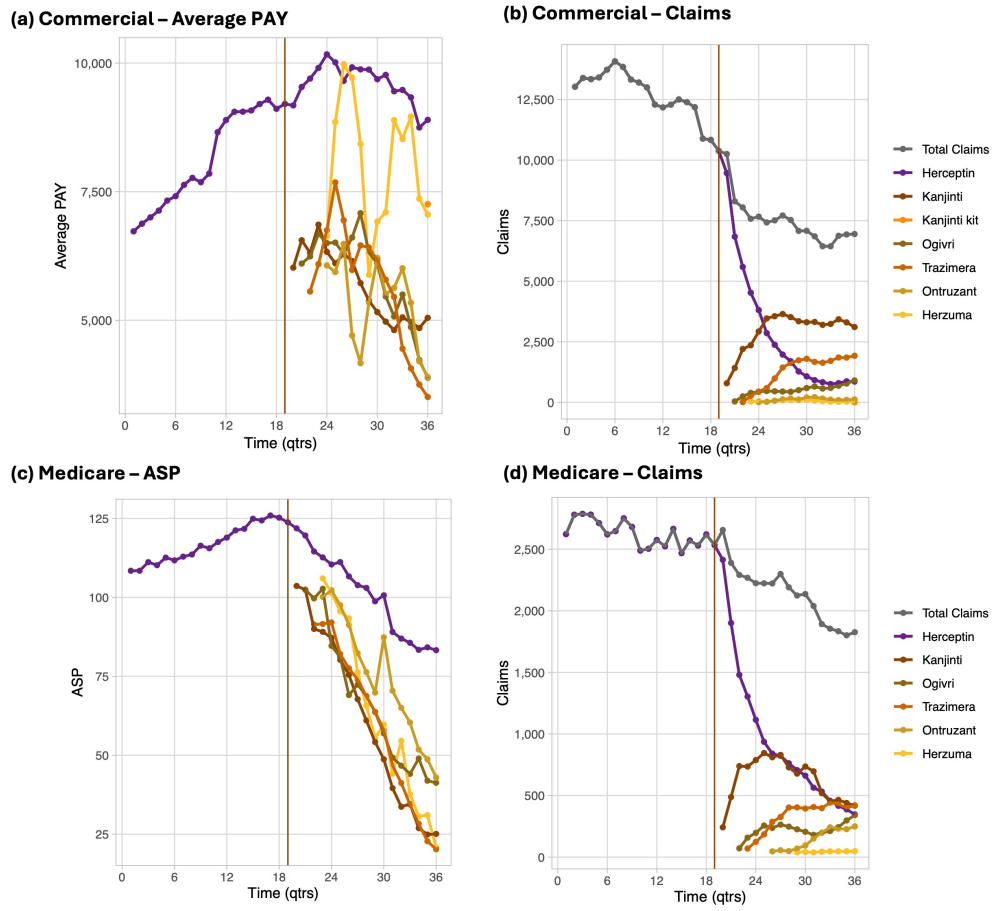
The vertical line on each graph indicates the quarter immediately prior to the first biosimilar entry. Biosimilar entry was defined as the first quarter in which a biosimilar product had both price (gross PAY for commercial, ASP for Medicare) and volume (claims) data available.

Trastuzumab

Trastuzumab reference product and biosimilar market dynamics (Figure 1-3) were very similar to the rituximab market – biosimilars entered at lower prices than the reference product Herceptin®

and declined more steeply in both the Medicare and Commercial datasets. The first biosimilar (Kanjinti®) gained substantial market share and Trazimera® was able to gain market share as well after 4-5 quarters. These findings are similar to those documented by Chen et al. for the period 2019-2020.[16]

Figure 1-3. Trastuzumab Commercial and Medicare Markets, 2015-2023



The vertical line on each graph indicates the quarter immediately prior to the first biosimilar entry. Biosimilar entry was defined as the first quarter in which a biosimilar product had both price (gross PAY for commercial, ASP for Medicare) and volume (claims) data available.

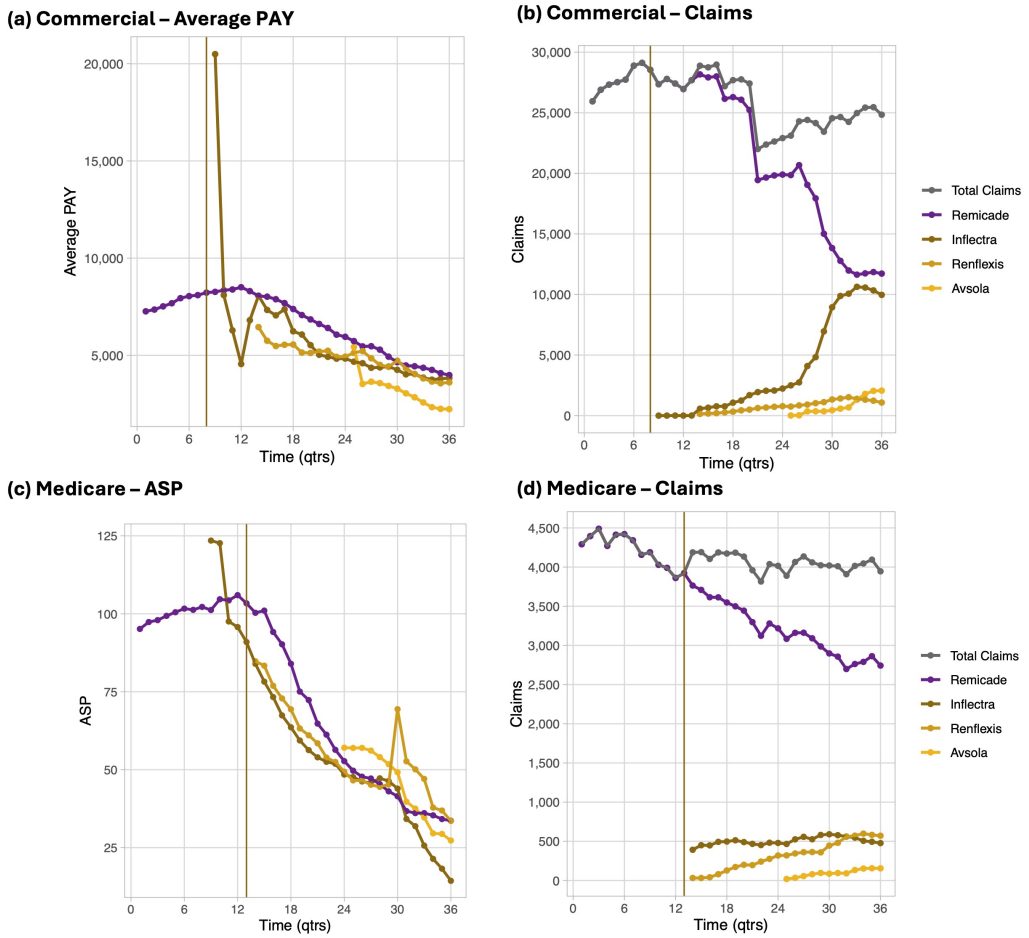
Infliximab

In Medicare, the infliximab reference product Remicade® competes with its biosimilars very closely on price (Figure 1-4). The biosimilars Renflexis® and Inflectra® entered the market in the same quarter (Inflectra® had an ASP available 5 quarters before Renflexis®, but no claims

recorded), resulting in an increase in total claims and an eventual decline in reference product market share, but the biosimilars overall still had trouble gaining market share over Remicade®, which still held 70% of the market at the end of 2023.

In commercial plans, the price dynamics are similar to Medicare – the reference product and biosimilar prices and trends track each other closely. However, the commercial sector differs from Medicare in that Inflectra® was able to gain substantial market share over Remicade®, converging to essentially split the market – Inflectra® having 40% of the market by the end of 2023 and Remicade® having 47%. The other biosimilar did not fare as well, with very small market share for Avsola®.

Figure 1-4. Infliximab Commercial and Medicare Markets, 2015-2023



The vertical line on each graph indicates the quarter immediately prior to the first biosimilar entry. Biosimilar entry was defined as the first quarter in which a biosimilar product had both price (gross PAY for commercial, ASP for Medicare) and volume (claims) data available.

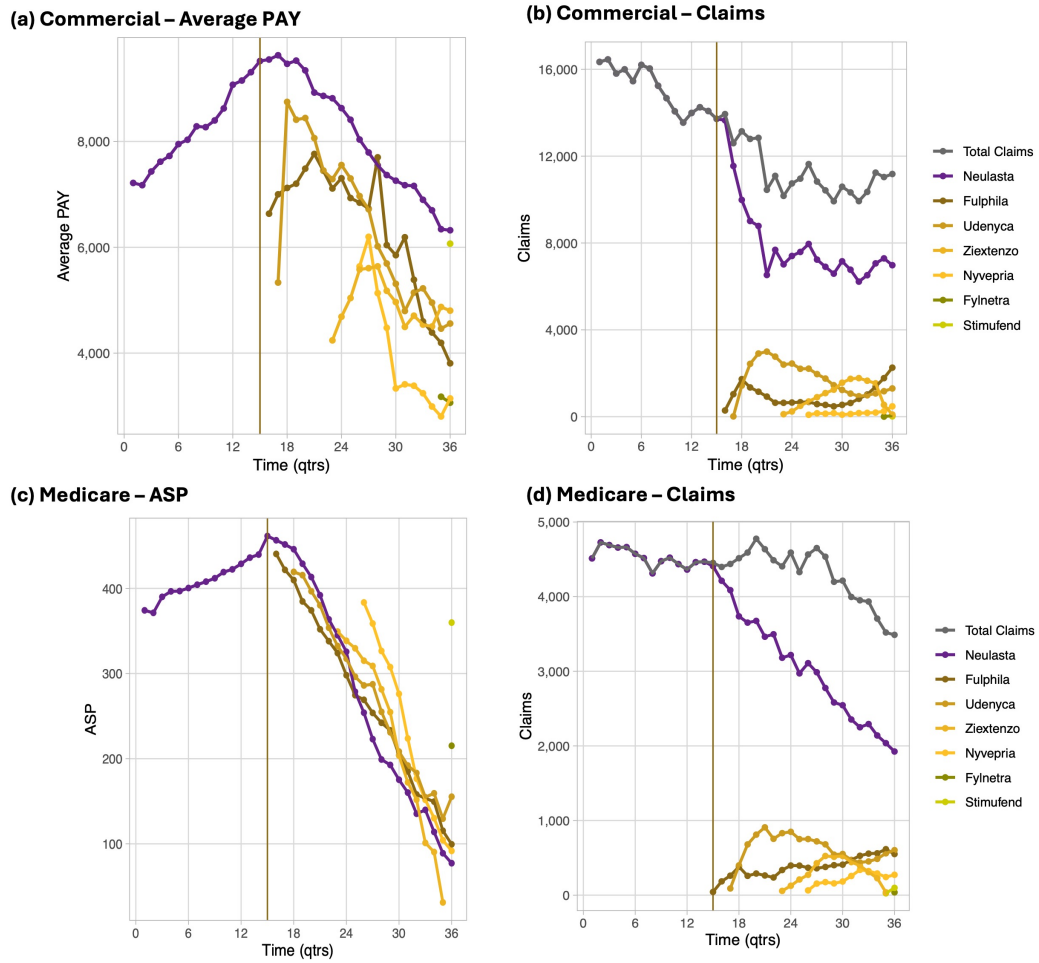
Pegfilgrastim

The pegfilgrastim market in Medicare appears similar to infliximab, with ASP of reference product Neulasta® and its biosimilars all tracking very closely (Figure 1-5). The market share trends were also similar, with Neulasta® losing substantial market share over time (down to 55% at the end of 2023) and the biosimilars gaining.

In commercial, however, the infliximab and pegfilgrastim markets differ. The pegfilgrastim biosimilars' prices were lower than Neulasta® and decline at approximately the same rate. The biosimilars Fulphila® and Udenyca® gained market share over Neulasta® at first, but then the

Neulasta® market share stabilized and it seemed that the biosimilars were competing more with each other for market share.

Figure 1-5. Pegfilgrastim Commercial and Medicare Markets, 2015-2023



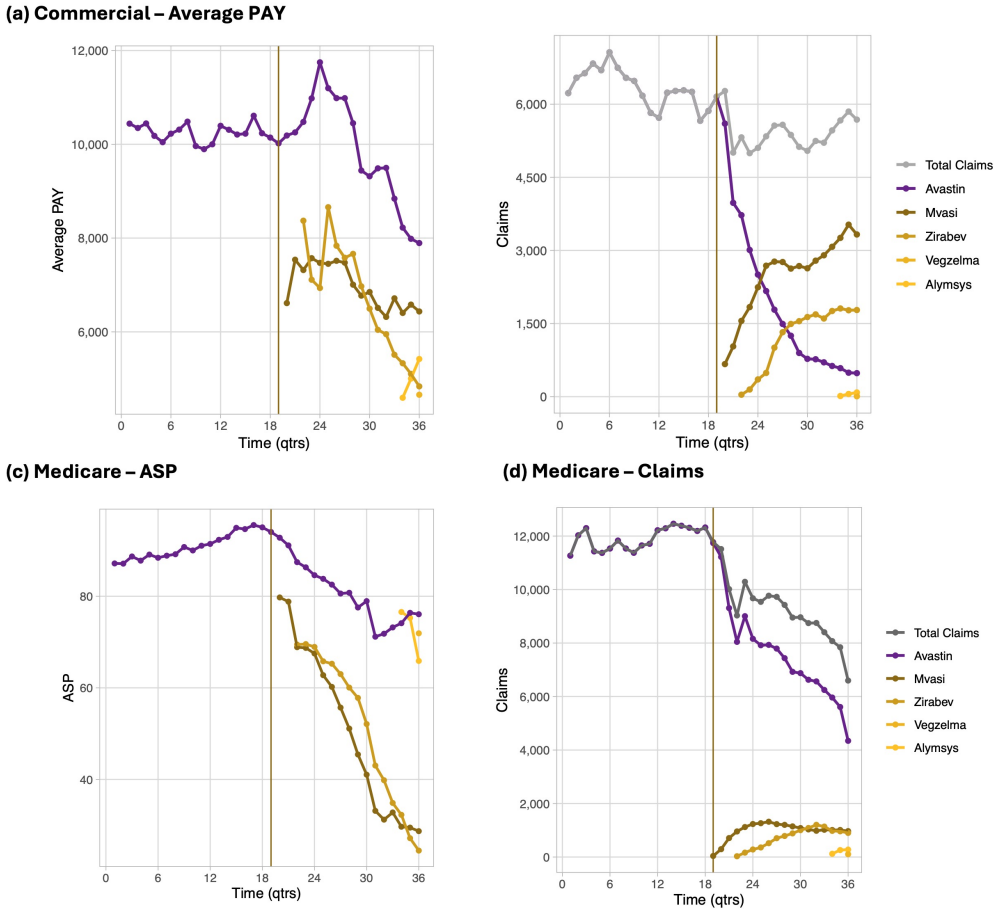
The vertical line on each graph indicates the quarter immediately prior to the first biosimilar entry. Biosimilar entry was defined as the first quarter in which a biosimilar product had both price (gross PAY for commercial, ASP for Medicare) and volume (claims) data available.

Bevacizumab

In both the commercial and Medicare bevacizumab markets (Figure 1-6), the biosimilars Mvasi® and Zirabev® both entered at lower prices than the reference product. However, while the biosimilars were able to overtake the reference product in market share substantially in the commercial market, the reference product maintained much of the market in Medicare. This

maintained market share may be due to the use of the reference product in ophthalmic indications, which were excluded in the commercial data but could not be separated out in the Medicare data.

Figure 1-6. Bevacizumab Commercial and Medicare Markets, 2015-2023



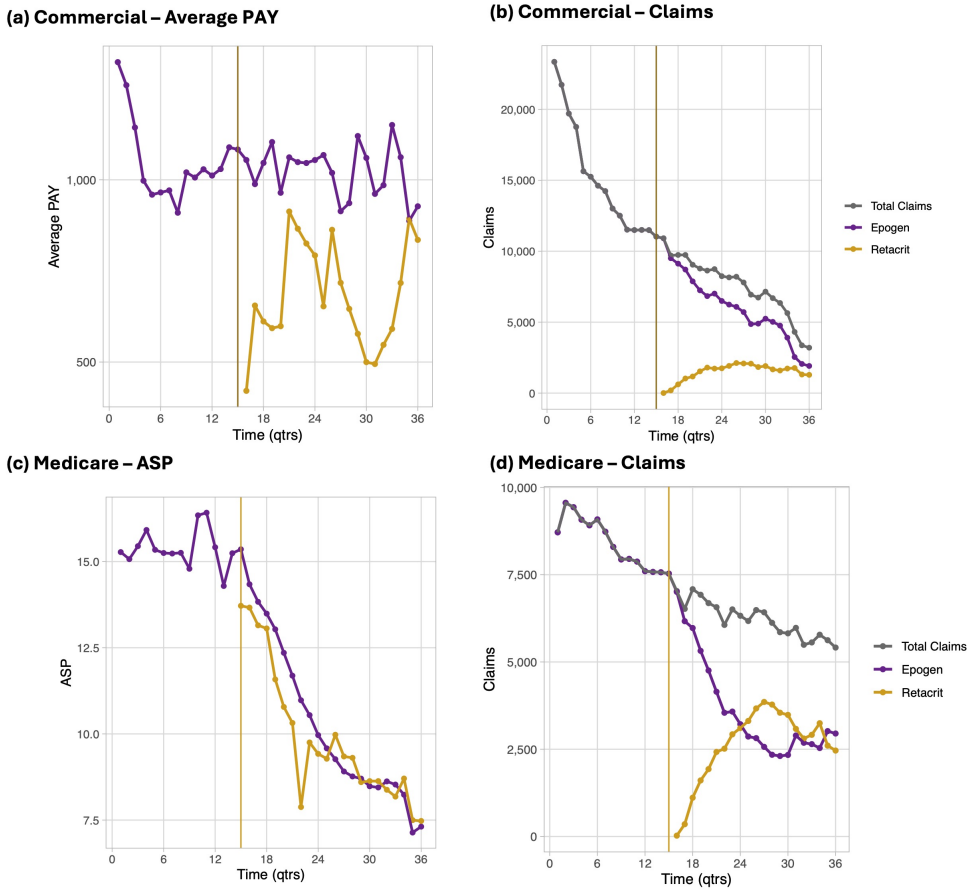
The vertical line on each graph indicates the quarter immediately prior to the first biosimilar entry. Biosimilar entry was defined as the first quarter in which a biosimilar product had both price (gross PAY for commercial, ASP for Medicare) and volume (claims) data available. In the Commercial dataset, bevacizumab claims with units equal or less than 2 (presumed ophthalmic use) were excluded.

Epoetin Alfa

There is only one biosimilar in the epoetin alfa market (Retacrit®). In Medicare, the reference product Epogen® and the biosimilar have similar ASPs and trend, and Retacrit® gained substantial market share (Figure 1-7). In commercial, however, the price for Retacrit® is substantially lower than Epogen® for most of the study period. Retacrit® increased in market share initially but then

stabilized and converged with Epogen® market share as overall claims for epoetin alfa declined, perhaps due to changing clinical guidelines or availability of alternatives.

Figure 1-7. Epoetin Alfa Commercial and Medicare Markets, 2015-2023



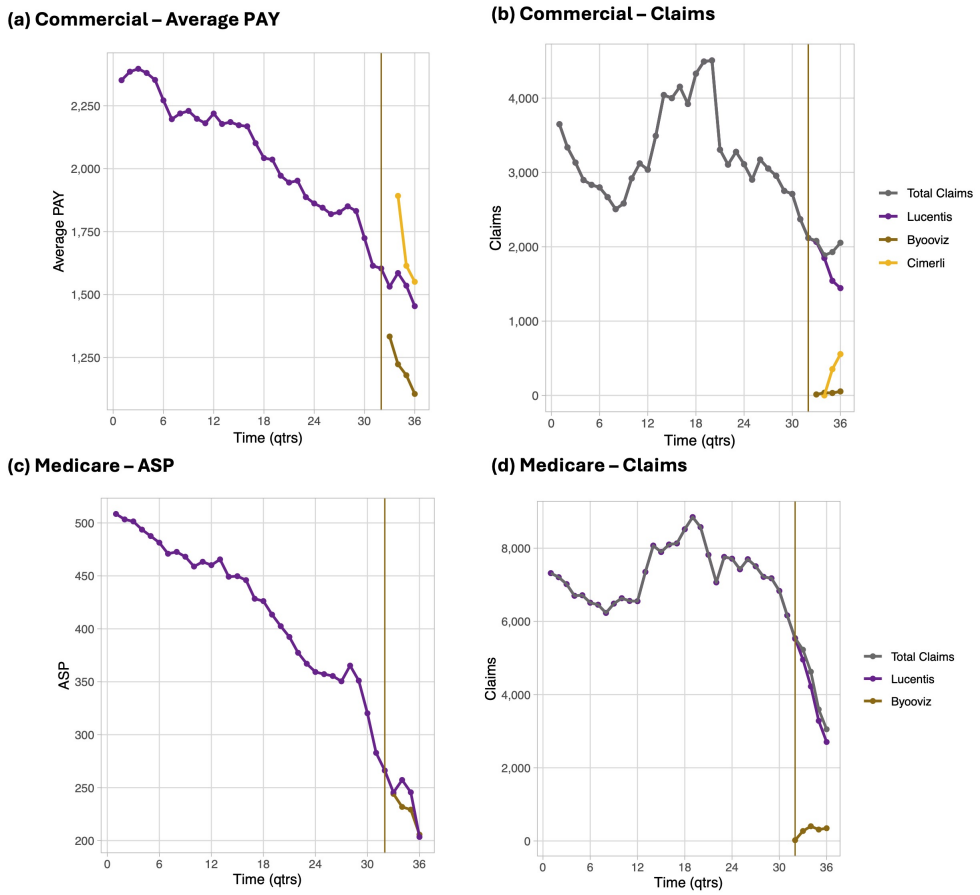
The vertical line on each graph indicates the quarter immediately prior to the first biosimilar entry. Biosimilar entry was defined as the first quarter in which a biosimilar product had both price (gross PAY for commercial, ASP for Medicare) and volume (claims) data available.

Ranibizumab

Biosimilars for ranibizumab have only recently entered the market, so discerning trends at this point is difficult. We can, however, see that in Medicare, Byooviz® entered the market at the same ASP as the reference product Lucentis®, while in commercial the price for Byooviz® was lower than Lucentis® (Figure 1-8). Our Medicare data did not include claims for Cimerli®, but we observe that in the commercial sector, Cimerli® entered at a higher price than Lucentis® but then dropped

quickly, and it has already been able to gain market share more than Byooviz®, despite entering later.

Figure 1-8. Ranibizumab Commercial and Medicare Markets, 2015-2023



The vertical line on each graph indicates the quarter immediately prior to the first biosimilar entry. Biosimilar entry was defined as the first quarter in which a biosimilar product had both price (gross PAY for commercial, ASP for Medicare) and volume (claims) data available.

Discussion

The quarterly price and market share trends indicate that in most cases, market behaviors in the two insurance populations differ within each drug market, and each of the drug markets are different from one another. Each biologics market is unique; insights from one market cannot necessarily be generalized to others. This is concerning for the sustainability of biosimilars markets because it highlights the significant uncertainty that manufacturers face when considering entering

a market with a new biosimilar product. In some cases, the first biosimilar to enter gained substantial market share, but subsequent products did not. In other cases, reference products were able to maintain significant market share despite biosimilars having lower prices. In at least one market, biosimilars were able to compete equally and each gain similar market share. These differences are likely due to differing reference product manufacturer strategy (pricing, rebates/discounts, advertising, provider outreach) and payer negotiations and preferences that limit biosimilar coverage or do not incentivize biosimilar use – these are not traditional consumer markets that are reacting to price changes. Thus, policy initiatives seeking to improve savings should seek to eliminate complexities and barriers that hinder biosimilar competition, such as changes to reimbursement structure, reducing patent litigation that delays biosimilar entry, and incentivizing uptake.

There are some limitations with this analysis, particularly in the commercial data. The MarketScan data does not include all payers in the US, so may not be generalizable to all commercial plans. We used the gross payments variable in the MarketScan data for the commercial data (PAY), which is the total amount paid to a provider for a service after applying discounts and before applying coordination of benefits and patient out-of-pocket. Though discounts are accounted for, it is unclear whether all types of discounts (such as rebates, which are often paid after point of sale) are included, and this also does not account for additional discounting and manufacturer incentives at the provider level. Additional limitations are shown in Table 1-2.

Table 1-2. Data Limitations and Adjustments

Limitation	Adjustment/Discussion
Commercial - MarketScan Data Negative PAY amounts	Some claims in the MarketScan data contain negative amounts that reflect adjustments to correct a payment error. These are largely resolved in the outpatient and pharmacy datasets and combined into one line, however they are not resolved in the inpatient services dataset and there are still some adjustment records remaining in all three. To avoid inflating counts of claims due to the presence of adjustment records, we summed financial variables for each patient and drug on a given service date and kept all non-zero PAY values. Thus, a "claim" was defined as a non-zero, non-negative payment for a drug on a given day.
Commercial – Pharmacy claims	Some claims are from the pharmacy dataset, potentially due to white- or brown-bagging, institutions or infusion centers connected to a pharmacy, or specific plans with these medications on the pharmacy instead of medical benefit. This means that the "price" for those in the pharmacy dataset is likely further complicated with Pharmacy Benefit Manager (PBM) involvement. Thus, the "prices" reported here may not be the real-world prices being paid for each of these drugs.
Commercial - Bevacizumab ophthalmic indication	One drug, bevacizumab, is used off-label for ophthalmic indications at a much lower dose than antineoplastic indications. The data show a disproportionate amount (higher) of reference product (Avastin) being used for ophthalmic indications compared to the biosimilars. This resulted in a lower average gross pay amount for the reference product. To correct for this, we used the "UNITS" variable in the MarketScan data to exclude claims for bevacizumab that were 2 or fewer (as bevacizumab is billed as one unit per eye for ophthalmic indications). However, this may have missed some, as the UNITS variable is not available from all data contributors in the dataset. This was not an issue in the Medicare data, as ASP is already a standardized per-billing-unit price.
Commercial – biologic dosing	Other than removing the bevacizumab ophthalmic indication where possible, we assumed that the reference products and biosimilars are being used at similar doses within each market, as the units and quantity reported in the claims are not available for all claims and are thus unreliable for standardizing cost per milligram or other unit.
Medicare - Biosimilar entry	Biosimilar entry was defined as the first quarter in which a biosimilar product had both price (ASP) and volume data available. There were two products for which an ASP was available prior to any claims (infliximab and epoetin alfa) and three products for which a few claims were present prior to an ASP (pegfilgrastim, bevacizumab, and ranibizumab).
Filgrastim – Granix (tbo-filgrastim)	Though Granix® (tbo-filgrastim) is another competitor, it was omitted because it was not approved through the biosimilar approval pathway.

Conclusion

These findings highlight the substantial differences in market dynamics in the existing biosimilar markets, which makes generalizing the effects of competition across markets difficult. Many factors such as indication-specific drug innovation, contracting, payer preferences, and provider and patient perceptions all impact biosimilar competition, but do so differently in each drug market. If manufacturers choose not to develop biosimilars or to exit established markets, there is potential for shortages and increased costs to patients and health care systems. Thus, it is important for policy makers to address barriers to biosimilar competition to preserve competition and increase savings.

Chapter 1b. Heterogeneous Price Decline and Reference Product Market Share after Biosimilar Entry in the United States

Abstract

Background

Understanding market share and pricing dynamics within the United States (U.S.) biosimilar markets is critical for anticipating future behavior and establishing a sustainable market that produces cost-savings for the healthcare system.

Methods

We examined eight biologics with biosimilars available in the U.S. in the Medicare and commercial health insurance populations using two datasets. We used linear regression to assess the relationship between reference product market share and each biosimilar entry and to study biosimilar versus reference product price decline since biosimilar entry.

Results

In Medicare, reference product market share declined consistently, though to varying degrees across molecule groups. In the commercial sector, market share trends were more variable.

Price trends differed substantially. In Medicare, biosimilars showed an 18.6% ($p<0.01$) greater price decline on average than reference products during the time after biosimilar entry (range of 4 to 32 quarters), while in commercial markets the overall result was not significant. Price decline patterns varied widely between the different biologics.

Conclusion

Due to differences between biologic markets in market share and price decline trends, it is challenging to generalize predictions or conclusions about biosimilar market behavior.

Stakeholders should pursue policies that support greater predictability and robust competition across biologic markets.

Introduction

Biosimilars

Biologic drugs are complex molecules that are expensive to develop and manufacture, leading to high prices. Biologics accounted for 45% of U.S. drug spending ($324 billion) in the U.S. in 2023.[6] Biologics are available for many therapeutic areas, but are most common in immunology, antidiabetics, and oncology.[2]

The Biologics Price Competition and Innovation Act (BPCIA) was enacted in 2010, providing a regulatory pathway for the approval of biosimilars.[17] Biosimilars are highly similar with no clinically meaningful differences from their reference products. Biosimilars are often available at lower prices than their reference products and produce savings by utilization of lower-priced products. Additionally, competition drives down prices overall, providing a significant opportunity for savings.[5,7,18] In Medicare Part B, biosimilar competition was estimated to reduce program spending and patient out-of-pocket costs by approximately 62% compared to projected spending without biosimilar competition in 2023.[19]

In the U.S., drugs are covered by commercial insurance plans under either the medical benefit or the pharmacy benefit. The medical benefit primarily covers services like hospitalizations and outpatient visits, but also covers any drugs administered in the hospital or outpatient setting.[20] In Medicare, the medical benefit that includes outpatient visits and medications administered by physicians in the outpatient setting is known as Part B.[21] The pharmacy benefit covers drugs that are dispensed at a pharmacy and taken home by the patient. In Medicare, the pharmacy benefit is referred to as Part D.[22]

Due to their complex structure biologics are typically injectable. Many can only be administered by physicians and thus are billed under the medical benefit (Part B in Medicare). Others are self-

injectable and can be billed under the pharmacy benefit (Part D in Medicare). The former are the focus of this study as they have been on the market longer than self-injectable and have publicly available reimbursement rates.

Reimbursement and Complex Market Dynamics

Drugs that are reimbursed through Medicare Part B for the Medicare population (typically patients aged >65 years plus some additional populations) based on Average Sales Price (ASP). ASP is the volume-weighted average price at which a manufacturer sells the product to any purchaser (with some exclusions) in the U.S. in a given calendar quarter.[23] Manufacturers report these sales to CMS for calculation of the ASP.[24] Providers are paid ASP plus an add-on, which is typically 6%. The Inflation Reduction Act changed this reimbursement for biosimilars to ASP + 8% of the reference product ASP if the ASP for the biosimilar is less than that of its reference product, as a means of incentivizing biosimilar use for a five-year period.[25] Each biosimilar has its own ASP, unlike the small molecule generics market that combines all branded and generic products of the same molecule into one ASP with the same reimbursement rate. This allows small molecules to compete more directly on price, while biosimilars and their reference products compete more like separate branded products and can result in physicians being incentivized to select higher-priced products to receive the higher reimbursement.[26]

The term "commercial insurance" is used to describe private insurance plans that are generally offered either through a patient's employer or purchased directly by the patient, typically patients under the age of 65. For commercial insurers, physician-administered biologics are typically billed under the medical benefit, with reimbursement rate structures like Medicare's ASP model rather than pharmacy pricing negotiated by a pharmacy benefit manager (PBM). However, there still may

be contracted discounts with plans. These reimbursement rates vary across health plans and are not publicly posted.

This process of physicians purchasing products and receiving reimbursement is referred to as "buy-and-bill". Providers can negotiate discounts from manufacturers for purchasing the product, to maximize the spread between their purchase price and the reimbursement rate. This means that in some cases, if a significant discount on a typically more expensive product (with therefore a higher reimbursement rate) can be negotiated, the provider is then incentivized to choose that higher priced product.[27] However, these provider discounts are factored into ASP and the ASP is continuously driven downward, which risks manufacturer incentives to develop biosimilars and remain in the market, as well as provider net cost recovery as the margins diminish over time.[28]

The variation in payment rates, arrangements with public and private payers, and heterogeneous provider contracts results in a complex and unpredictable market with prices that decline precipitously in some markets. In the generics market, there are rapid and dramatic price decreases, with product prices bottoming out near marginal cost of production, contributing to drug shortages.[5,29,30] Biosimilars are more expensive to manufacture than generics and the approval process is more rigorous, leading to smaller profit margins and barriers to entry. Thus, as the biosimilars market is still young, it is important to ensure that pitfalls that are being observed in the generics market do not happen with biosimilars as well, and that barriers and complexities can be addressed to improve competition, ensure sustainability, and preserve savings in biologics markets.

Existing Literature

Previous studies that have examined price and utilization of biosimilars often look at multiple drug markets in the time since biosimilar launch, and show that there is substantial variation in market

behaviors across drug products.[31–34] Because the first biosimilar was only approved in 2015, this is a new and ever-evolving market in which research is quickly out of date. With more biosimilars entering the market each year, research must continually update to elucidate trends and understand patterns to predict future market dynamics and identify areas to improve competition and the sustainability of biosimilars to ensure continued For example, four biosimilars were launched in 2022, thirteen biosimilars were launched in 2023, and two in 2024—illustrating the dynamic market and that continuous reevaluation of market trends is important.[35]

There are a few studies examining the relationship between biosimilar competition and uptake/market share or price that only report on one or two molecules and generally only in one insurance population, rather than comparing across available biosimilar markets.[16,36–38] These studies further shed light on the fact that biosimilar markets differ substantially. However, it is also important for stakeholders to understand how these markets behave compared to one another as well as across insurance sectors, to know where generalizations can and cannot be made. Understanding these markets can help manufacturers with development decisions, can help policy-makers know where change needs to be made to improve predictability and sustainability, and can give payers context for decisions that improve savings.

The key gaps in the existing research include limited comparisons between payer types (i.e. Medicare and commercial) for medical benefit biologics, limited multi-biologic market analyses, and to our knowledge none have examined the rate of price decline. The rate of price decline in biosimilars compared to their reference products is important to understand to identify ways to strengthen competition for prices to come down more synchronously and avoid the bottoming-out phenomenon being observed in the generics market. This study aims to address these gaps.

Objectives

The objective of this study is to provide a systematic analysis of biosimilar competition in both Medicare and commercial sectors. Specifically, we 1) examine quarterly trends in reference product market share across eight biologic markets after biosimilar entry, separately for Medicare and commercial populations, 2) analyze price trajectories post-biosimilar entry, to identify whether biosimilar prices decline relative to reference products and how those patterns differ by drug group and sector, and 3) highlight heterogeneity in market dynamics to draw implications for policy to improve biosimilar market sustainability.

This work contributes evidence on the heterogeneity of biosimilar competition to inform and motivate policymakers and payers to make decisions that foster a more robust biosimilars market.

Methods

Data Sources

We examined quarterly price and market share in the Medicare and commercial health insurance populations from the time of initial biosimilar market entry in the first quarter of 2015 through the fourth quarter of 2023. For Medicare, we used quarterly average sales price (ASP) data from the Centers for Medicare and Medicaid Services (CMS) Drug Pricing Files along with volume data from the standard Medicare Limited Data Set (5% sample) for the following biologics: filgrastim, rituximab, infliximab, trastuzumab, pegfilgrastim, epoetin alfa, bevacizumab, and ranibizumab.[12,13] The full list of products included and the associated codes used to identify each product are in the Supplemental Appendix A, Section A1. Biosimilar entry was defined as the first quarter in which a biosimilar product had both price (ASP) and volume data available. There were two products for which an ASP was available prior to any claims (infliximab and epoetin alfa) and

three products for which a few claims were present prior to an ASP (pegfilgrastim, bevacizumab, and ranibizumab).

For the commercial insurance population, we used the CMS Drug Pricing Files crosswalk (HCPCS to NDC codes) for each quarter plus any additional NDC codes identified in Merative™ Micromedex® RED BOOK® Online to identify claims for the drugs of interest in the Merative™ MarketScan® Commercial Database.[12,14] We used gross payments to a provider ("PAY") as the price, which is the amount eligible for payment under the medical plan terms (inclusive of patient cost-sharing) after applying rules such as discounts. Biosimilar entry was defined as the first quarter in which a biosimilar product had claims with a non-zero average gross payment amount.

Gross payments and ASP were both adjusted for inflation to Q4 2024 using the Medical Care CPI.[15]

Using the price and volume in each data source, we graphed each of the reference products and their biosimilars over our study period. The graphs and descriptions are included in Chapter 1a.

Biosimilar Entry & Market Share

We assessed reference product market share over time after biosimilar entry using two linear regression models. The first assesses the incremental change in reference product market share with each biosimilar entry and is described in detail in the Supplemental Appendix A, Section A2. The second regression model is similar (Equation 1), to assess the cumulative relationship between the number of biosimilars on the market with the reference product market share. The covariate $\boldsymbol{biosims_t}$ is a categorical variable for the number of biosimilars on the market for a given group in each quarter (**t**), and thus the interpretation of the coefficient for each biosimilar entrant is the cumulative change in reference product market share associated with that biosimilar entrant. We

used this model for each drug group individually, as well as in the overall data with fixed effects for drug group.

$$\textbf{Equation 1. } \boldsymbol{Ref\ product\ Mktshare = \beta_0 + \beta_1 biosims_t + \beta_2 log(TotalClaims)_{gt} + \varepsilon}$$

Price Decline

We assessed biosimilar versus reference product price decline over time since biosimilar entry using a linear regression with price ratio as the outcome (Equation 2). Price ratio is the price in each quarter (***t***) divided by the base price. For reference products, base price was defined as the price in the quarter immediately prior to the first biosimilar entry. For biosimilars, base price was defined as the price in the first quarter of that biosimilar's launch.

$$\textbf{Equation 2. } \boldsymbol{Price\ ratio_t = \beta_0 + \beta_1 Quarter_t + \beta_2 Bio_t + \beta_3 log(basePrice)_{gt} + \varepsilon}$$

The covariate $\boldsymbol{Quarter_t}$ is linear time (quarterly) and Bio_t is an indicator set to 1 for biosimilars and 0 for reference products. Because of the large variance in price across markets, we controlled for $\boldsymbol{log(basePrice)_{gt}}$ for each biologic group (*g*) in each quarter (*t*). We used this model for each drug group individually, as well as in the overall data with fixed effects for drug group. Thus, $\boldsymbol{\beta_1}$ can be interpreted as price ratio slope (quarterly) for reference products, $\boldsymbol{\beta_1 + \beta_2}$ is price ratio slope for biosimilars, with $\boldsymbol{\beta_2}$ indicating the rise or decline over and above reference products.

Results

Sample

Over the 36-quarter study period, the Medicare data included 1,503,570 claims across the eight drug groups, with an average of 41,766 claims (24,658 individuals) in each quarter. The

commercial data included 2,905,900 claims across the eight drug groups, with an average of 78,538 claims (29,802 individuals) in each quarter.

The total number of claims within each quarter for each biologic group was used to calculate the reference product market share, using number of claims for the reference product divided by total number of claims for the biologic group.

Biosimilar Entry & Market Share

The results of the regression to assess the incremental change in reference product market share are presented in full in the Supplemental Appendix A, Section A2. In the overall analysis with fixed effects for drug group in the Medicare sector, only the first and fifth biosimilar entries were statistically significant, with an associated 13.7% and 15.9% decrease in reference product market share, respectively. There was substantial variation in the point estimates within each biosimilar entry. For example, the first biosimilar entry was associated with between a 5.4% (pegfilgrastim) and a 34.2% (filgrastim) decrease in reference product market share. In the commercial sector, more of the overall results were statistically significant (only the first and sixth were not), but there was still substantial variation when the biologic markets were examined individually.

The results identifying cumulative change in reference product market share illustrate these market differences more clearly and are shown in Table 1-3, Figure 1-9, and Figure 1-10.

In the Medicare sector (Figure 1-9), reference product market share declined at a somewhat constant rate in most markets, though to varying degrees across markets. The commercial sector (Figure 1-10) has more variation across markets, with reference product market share plateauing and remaining stable in some markets (pegfilgrastim) and others with a steeper decline (rituximab, bevacizumab).

Filgrastim had three biosimilars enter the market. With the first biosimilar entry, reference product market share declined 34.2% ($p<0.01$) in the Medicare sector but only 19.6% ($p<0.01$) in the commercial sector. The second biosimilar entry was associated with a total reference product market share decline of 50.7% ($p<0.01$) and 29.1% ($p=0.022$) in Medicare and commercial, respectively. The effect of the third biosimilar is difficult to interpret, as there were only three quarters of data available and thus there may be additional effect on reference product market share with more time on the market.

Pegfilgrastim had six biosimilars enter the market (five and six entered at the same time in Medicare). In Medicare, entry of the first biosimilar was only associated with a 5.4% ($p<0.01$) decline in reference product market share, with an eventual total decline in reference product market share of 38.5% ($p<0.01$) by the fifth/sixth biosimilar. In the commercial sector, the first and second biosimilars entered only one quarter apart and therefore the point estimate for the first biosimilar was not statistically significant. The presence of two biosimilars was associated with a 22.7% ($p<0.01$) lower reference product market share, but reference product market share plateaued and declined only very slowly with subsequent biosimilars, with a total eventual decline of only 31.7% ($p<0.01$) for the sixth biosimilar. There were only two quarters of data for the fifth and one quarter of data for the sixth biosimilar in the commercial data.

Epoetin alfa only has one biosimilar on the market. In the Medicare sector, the two products essentially split the market by the end of the study period, but because the reference product market share initially declined and then regained some, the point estimate was not statistically significant. In the commercial sector, the presence of the one biosimilar was only associated with a 7.4% ($p=0.046$) decrease in reference product market share, likely due to the overall number of claims

for epoetin alfa products declining significantly over the course of the study period (over 10,000 at the time of biosimilar entry, declined to approximately 4,000 by the end of the study period).

Trastuzumab had five biosimilars enter the market during the study period. This appears as six in the commercial market due to the launch of an additional version of trastuzumab-anns (Kanjinti, Amgen, Inc., Thousand Oaks, CA) referred to as "Kanjinti Kit". In the Medicare sector, biosimilars were associated with a significant decline in reference product market share, with the first biosimilar associated with a 13.1% ($p<0.01$) decrease and very consistent further decline to an eventual total 61.3% ($p<0.01$) reduction in reference product market share. This effect does appear to begin to slow between the fourth and fifth biosimilar, indicating that reference product market share may begin to stabilize. In the commercial sector, the first three estimates are not statically significant, likely due to the first four biosimilars entering only one quarter apart. The sixth product entry was associated with an eventual total reference product market share decline of 65.6% ($p<0.01$).

Infliximab had three biosimilars enter during the study period. In the Medicare sector, the first and second biosimilars entered at the same time based on our definition (infliximab-dyyb had an ASP available for 5 quarters before any claims appeared). The presence of those first two biosimilars was associated with a 14.9% lower reference product market share ($p<0.01$), and the third with a 26.5% ($p<0.01$) reduction. In the commercial sector, the first biosimilar had very little (and statistically insignificant) effect on reference product market share, the second was associated with a 6.9% ($p<0.01$) reduction in reference product market share, and the third was associated with a 38.2% ($p<0.01$) reduction.

Rituximab had three biosimilars enter the market during the study period. In the Medicare sector, the first two biosimilars entered only two quarters apart which may contribute to the estimate for

the first biosimilar being statistically insignificant. The reference product market share declined steeply after that, with the second biosimilar entry being associated with a 33.9% ($p<0.01$) decline down to a total decline of 51.6% ($p<0.01$) with the third. The commercial sector was similar, but with an even steeper decline to a total reduction of 75.9% ($p<0.01$) with the third biosimilar.

Bevacizumab had four biosimilars enter the market during the study period, and the decline in reference product market share was substantially different between the Medicare and commercial sectors. In Medicare, the total reduction in reference product market share was only 12.8% ($p=0.057$). This may be partially due to the overall claims for bevacizumab declining after the first biosimilar entry, in addition to the inability to exclude claims where bevacizumab was used for ophthalmic indications, which are more commonly the reference product. In commercial, however, we were able to exclude most claims for ophthalmic uses, and the reference product market share declined by 69.2% ($p<0.01$) with the second biosimilar and even further declined by a total of 91.7% ($p<0.01$) by the end of the study period (4^{th} biosimilar).

Lastly, ranibizumab had one biosimilar in Medicare and two biosimilars in commercial enter the market during the study period. There were so few quarters of data available for these biosimilars because they are so new, so the results are difficult to interpret. In Medicare, there was a slight decline in reference product market share of 6.6% ($p<0.01$), and in commercial there was a total decline of 17.7% ($p=0.016$) with the two biosimilars.

Table 1-3. Additive Change in Reference Product Market Share, Each Biosimilar Entry

	Medicare			Commercial		
Group	**Estimate**	**SE**	**P**	**Estimate**	**SE**	**P**
One Biosimilar						
Overall	**-0.137**	**0.05437**	**0.039**	-0.051	0.05797	0.408
Filgrastim	**-0.342**	**0.06818**	**<0.001**	**-0.196**	**0.06103**	**0.003**
Pegfilgrastim	**-0.054**	**0.01566**	**0.001**	-0.006	0.01007	0.579
Epoetin Alfa	-0.152	0.09215	0.108	**-0.074**	**0.0357**	**0.046**
Trastuzumab	**-0.131**	**0.0277**	**<0.001**	-0.0002	0.04294	0.996
Infliximab	*N/A*	*N/A*	*N/A*	0.001	0.00192	0.761
Rituximab	-0.034	0.02194	0.135	**-0.147**	**0.06301**	**0.025**
Bevacizumab	-0.011	0.01064	0.300	**-0.159**	**0.04858**	**0.002**
Ranibizumab	**-0.066**	**0.01416**	**<0.001**	**-0.011**	**0.00365**	**0.006**
Two Biosimilars						
Overall	**-0.261**	**0.06644**	**0.006**	**-0.34**	**0.12902**	**0.034**
Filgrastim	**-0.507**	**0.11148**	**<0.001**	**-0.291**	**0.12148**	**0.022**
Pegfilgrastim	**-0.22**	**0.01518**	**<0.001**	**-0.227**	**0.05181**	**<0.001**
Trastuzumab	**-0.298**	**0.01405**	**<0.001**	-0.021	0.08298	0.805
Infliximab	**-0.149**	**0.00993**	**<0.001**	**-0.069**	**0.01396**	**<0.001**
Rituximab	**-0.339**	**0.05939**	**<0.001**	**-0.384**	**0.07077**	**<0.001**
Bevacizumab	**-0.107**	**0.02396**	**<0.001**	**-0.692**	**0.05926**	**<0.001**
Ranibizumab	*N/A*	*N/A*	*N/A*	**-0.177**	**0.0701**	**0.016**
Three Biosimilars						
Overall	**-0.357**	**0.07635**	**0.002**	**-0.519**	**0.10498**	**0.002**
Filgrastim	-0.281	0.2369	0.243	**-0.35**	**0.12273**	**0.007**
Pegfilgrastim	**-0.292**	**0.00965**	**<0.001**	**-0.24**	**0.04282**	**<0.001**
Trastuzumab	**-0.435**	**0.04221**	**<0.001**	-0.139	0.08884	0.127
Infliximab	**-0.265**	**0.01144**	**<0.001**	**-0.382**	**0.04832**	**<0.001**
Rituximab	**-0.516**	**0.03193**	**<0.001**	**-0.759**	**0.06315**	**<0.001**
Bevacizumab	**-0.127**	**0.03959**	**0.003**	**-0.908**	**0.02198**	**<0.001**
Four Biosimilars						
Overall	**-0.418**	**0.06567**	**<0.001**	**-0.388**	**0.11935**	**0.014**
Pegfilgrastim	**-0.371**	**0.01307**	**<0.001**	**-0.275**	**0.04428**	**<0.001**
Trastuzumab	**-0.572**	**0.01897**	**<0.001**	**-0.214**	**0.10027**	**0.04**
Bevacizumab	**-0.128**	**0.05746**	**0.032**	**-0.917**	**0.02368**	**<0.001**
Five Biosimilars						
Overall	**-0.578**	**0.0701**	**<0.001**	**-0.636**	**0.09527**	**<0.001**
Pegfilgrastim	**-0.385**	**0.02002**	**<0.001**	**-0.278**	**0.03801**	**<0.001**
Trastuzumab	**-0.613**	**0.03128**	**<0.001**	**-0.569**	**0.12988**	**<0.001**
Six Biosimilars						
Overall	*N/A*	*N/A*	*N/A*	**-0.575**	**0.1735**	**0.013**
Pegfilgrastim	*N/A*	*N/A*	*N/A*	**-0.317**	**0.03647**	**<0.001**
Trastuzumab	*N/A*	*N/A*	*N/A*	**-0.656**	**0.11677**	**<0.001**

Figure 1-9. Change in Reference Product Market Share with Each Biosimilar Entry, Medicare (Cumulative)

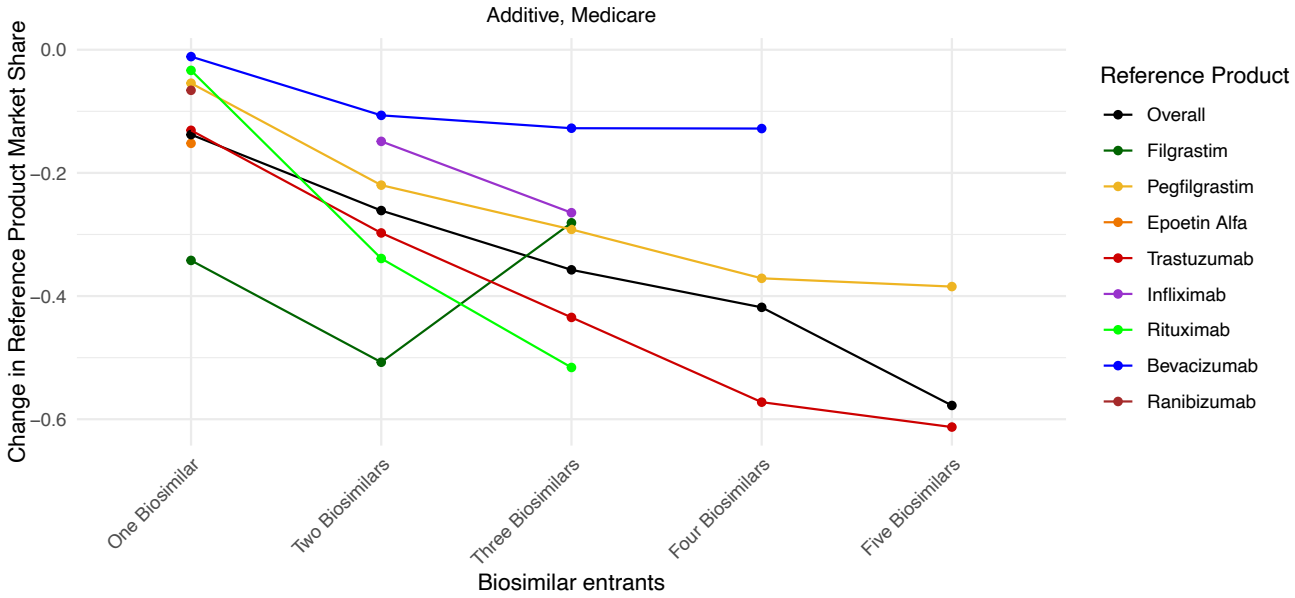
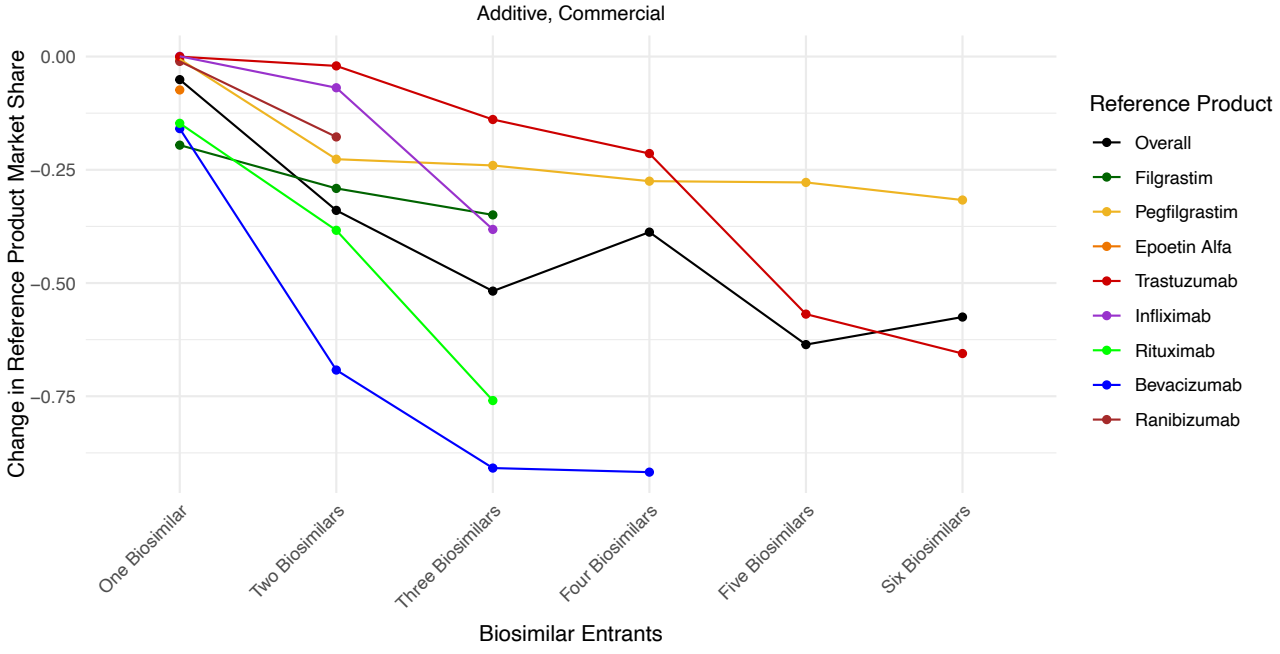


Figure 1-10. Change in Reference Product Market Share with Each Biosimilar Entry, Commercial (Cumulative)



Price Decline

The price decline trends in the Medicare and commercial sectors differ substantially. In the overall analysis, the estimate of 18.6% price decline for biosimilars over and above reference product price decline was statistically significant ($p<0.01$) over the course of the study period (differing durations since biosimilar entry by group, ranging from 4 quarters to 32), indicating that we reject the null hypothesis that there is no difference in price decline between biosimilars and reference products. In commercial, however, the result was not significant, indicating that we cannot reject the null hypothesis of no difference (Table 1-4).

Similar to the reference product market share results, the price decline results varied substantially when we looked at each individual market. The overall results and each market are shown in Table 1-4, Figure 1-11 (Medicare), and Figure 1-12 (commercial). In Medicare, biosimilars experienced a faster rate of price decline than reference products in five markets (filgrastim, trastuzumab, infliximab, rituximab, and bevacizumab), with two biosimilar markets having no statistically significant difference from reference products (pegfilgrastim, ranibizumab), and only one biosimilar market declining slower than its reference product (epoetin alfa). In commercial, there were only two biosimilar markets that experienced a faster rate of price decline than their reference products (infliximab, bevacizumab). Three markets had no statistically significant difference from reference products (pegfilgrastim, rituximab, ranibizumab), and three biosimilar markets had prices decline more slowly than reference products (filgrastim, epoetin alfa, and trastuzumab). We conducted a leave-one-out analysis to identify whether a particular biologic was driving the results in the overall analysis, which is described in the Supplemental Appendix A, Section A3.

Table 1-4. Price Ratio Decline, Regression Results

		Medicare			Commercial		
Group	**Coefficient**	**Estimate**	**SE**	**P**	**Estimate**	**SE**	**P**
Overall	Time (qtr)	**-0.027**	**0.00371**	**<0.001**	**-0.015**	**0.00395**	**<0.001**
	Biosimilar	**-0.186**	**0.04868**	**<0.001**	-0.063	0.10184	0.538
Filgrastim	Time (qtr)	-0.018	0.00773	0.098	-0.013	0.00902	0.241
	Biosimilar	**-0.410**	**0.02206**	**<0.001**	**0.582**	**0.21868**	**0.076**
Pegfilgrastim	Time (qtr)	**-0.043**	**0.00364**	**<0.001**	**-0.030**	**0.00694**	**0.005**
	Biosimilar	-0.003	0.01644	0.876	-0.111	0.08812	0.253
Epoetin Alfa	Time (qtr)	-0.020	0.00187	0.059	0.001	0.00498	0.736
	Biosimilar	**0.049**	**0.00000**	**<0.001**	**0.675**	**0.00000**	**<0.001**
Trastuzumab	Time (qtr)	**-0.045**	**0.00692**	**0.001**	**-0.017**	**0.00483**	**0.011**
	Biosimilar	**-0.232**	**0.08207**	**0.037**	0.365	0.32139	0.300
Infliximab	Time (qtr)	**-0.026**	**0.00340**	**0.005**	**-0.019**	**0.00372**	**0.015**
	Biosimilar	**-0.047**	**0.00374**	**0.001**	**-0.116**	**0.03892**	**0.048**
Rituximab	Time (qtr)	**-0.034**	**0.00993**	**0.04**	**-0.021**	**0.00447**	**0.018**
	Biosimilar	**-0.234**	**0.02192**	**0.002**	0.023	0.02381	0.404
Bevacizumab	Time (qtr)	-0.025	0.01234	0.117	**-0.020**	**0.00401**	**0.007**
	Biosimilar	-0.304	0.16912	0.147	**-0.27**	**0.04614**	**0.004**
Ranibizumab	Time (qtr)	**-0.050**	**0.00201**	**0.026**	-0.045	0.02086	0.163
	Biosimilar	**0.039**	**0.00000**	**<0.001**	**-0.041**	**0.0055**	**0.017**

qtr: Calendar quarter (3-months)

Figure 1-11. Medicare – Biosimilar Price Decline Compared to Reference Products

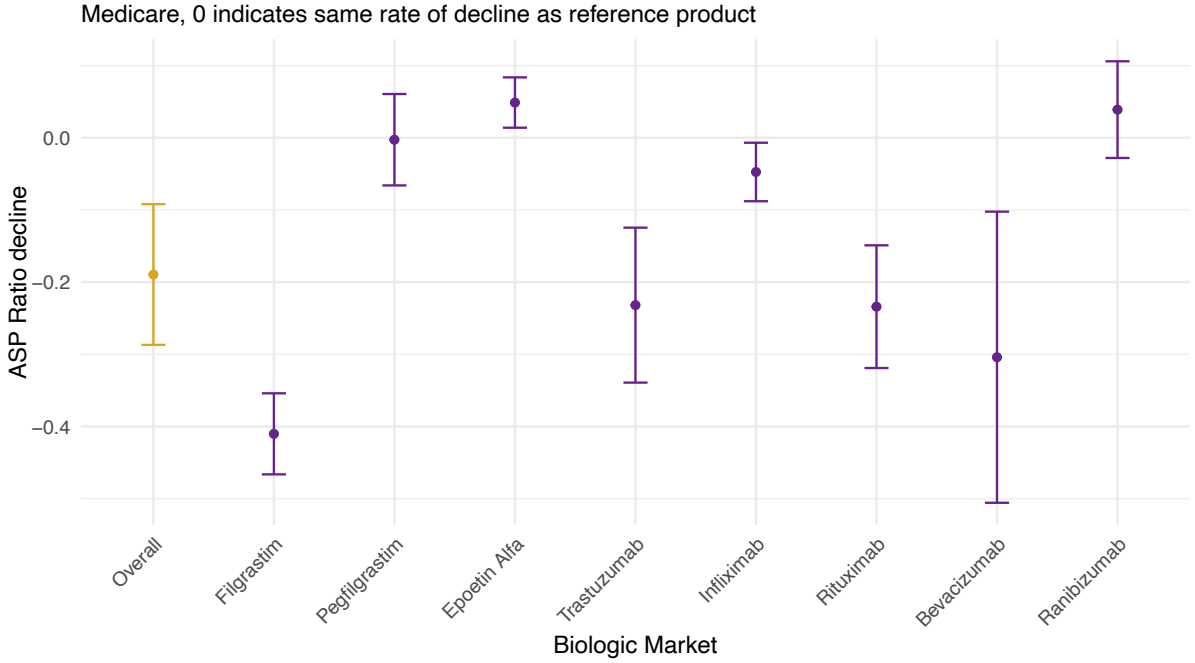
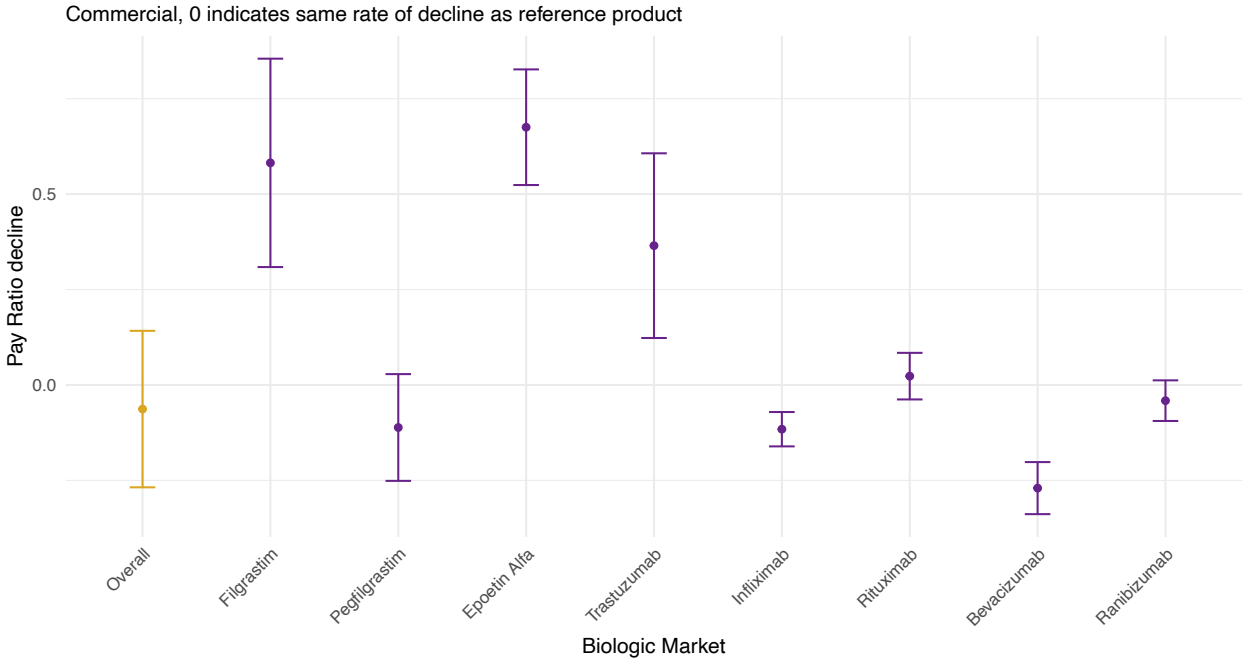


Figure 1-12. Commercial – Biosimilar Price Decline Compared to Reference Products



Discussion

We examined market share and price trends for eight biologics and their biosimilars in the Medicare and commercial health care sectors. Reference product market share declined in most markets after biosimilar entry, but the rate and pattern of this decline varied substantially across drug groups and between sectors. Some markets declined initially but then plateaued, others showed sustained reference product market share decline. Price dynamics were also heterogeneous, with biosimilar prices declining more steeply than reference products in the Medicare but not in the commercial sector. Price trends also differed markedly across biologic groups. These findings highlight the heterogeneity of competition in U.S. biosimilar markets and the limitations of drawing generalized conclusions about the effects of biosimilar entry or how a given market may behave in the future.

These results align with previous publications illustrating that biosimilar uptake and pricing in the U.S. is varied across drug markets and can be difficult to generalize.[4,34] There are negotiations, contracts, and differences in manufacturer pricing strategies that result in actual prices being confidential and variable, thus makes sense that market share and price trends differ across markets. Manufacturers of both biosimilars and reference products have differing strategies and may be giving discounts, rebates, provider education/outreach, or running direct-to-consumer ads, all of which impact uptake. Additionally, provider financial considerations such as net cost recovery can result in incentives to select higher-priced reference products over lower-priced biosimilars.[28] Patient and prescriber preferences such as hesitation to switch between reference products and biosimilars is difficult to measure and can affect uptake as well.[39,40] These complex market dynamics occur to a greater degree than in the small molecule brand/generics markets due to biosimilars having their own brand names and reimbursement rates and essentially competing from the consumer perspective as if they're a separate product.[3,26]

Policy and Market Implications

The key takeaway of this study is that there is substantial product-level variation, and thus caution should be used in aggregating estimates of biosimilar market dynamics. The price and market share reactions to each biosimilar entry were quite different by market, indicating that it is difficult to predict what may happen with the next. This is potentially concerning from the manufacturer's perspective, as there is no guarantee that a new product will capture market share even if prices are lower. Manufacturers are also targeting larger and higher-spend markets, in order to ensure profitability even if only a small market share is captured.[6] These considerations are compounded by the threat of patent litigation, which can further delay the entry of biosimilars. There have been two biosimilars approved in 2016 and 2019 for Enbrel, for example, which have been blocked

from the market until 2029 due to patent litigation.[41(pp0-3)] The barriers to competition and the unpredictability of these markets may lead to manufacturers deciding not to develop biosimilars,[42] or manufacturers deciding to leave the market, which may have been the case for the pegfilgrastim biosimilar pegfilgrastim-bmez (Ziextenzo, Sandoz Inc., Princeton, NJ), which did not have an ASP between Q2 2023 and Q1 2025.[12] While the biosimilars market has not yet experienced the severe price declines and shortages seen in small molecule generics, current trends suggest this risk may not be far off. Prevention or removal of biosimilar competitors has the potential to cause shortages, reduce competition, and increase costs to patients and healthcare systems.

As prices decline and uptake of biosimilars is slow, there is concern that the biosimilars market is not sustainable and the savings experienced to date may be at risk.[3,43] It is important to understand how these markets do behave and to identify lessons to enact policy that will improve the sustainability of the biosimilars market in the U.S.by encouraging manufacturers to pursue biosimilar development and to increase uptake of biosimilars.

Limitations

This study has a few limitations. Both data sources (Medicare 5% sample and MarketScan data) do not include all payments and claims in the U.S. and therefore may not be generalizable to all Medicare and commercial plans. This analysis is descriptive and identifies associations rather than causal effects of biosimilar entry, and thus these market changes cannot be specifically attributed to biosimilar entry.

One drug, bevacizumab, is used off-label for ophthalmic indications at a much lower dose than antineoplastic indications. The data show a disproportionate amount (higher) of reference product (Avastin, Genentech, Inc., South San Francisco, CA) being used for ophthalmic indications compared to the biosimilars. This resulted in a lower average gross pay amount for the reference

product. To correct for this, we used the "UNITS" variable in the MarketScan data to exclude claims for bevacizumab that were 2 or fewer (as bevacizumab is billed as one unit per eye for ophthalmic indications). However, this may have missed some, as the UNITS variable is not available from all data contributors in the dataset. This was not an issue in the Medicare data, as ASP is already a standardized per-billing-unit price. Other than removing the bevacizumab ophthalmic indication where possible, we assumed that the reference products and biosimilars are being used at similar doses within each market, as the units and quantity reported in the claims are not available for all claims and are thus unreliable for standardizing cost per milligram or other unit.

The difference in price decline trends between Medicare and commercial in our analysis is likely due to the difference in prices used. In our Medicare analysis, most discounts/rebates are accounted for due to their incorporation into ASP, and thus the data exhibits a more real-world representation of the average prices of each drug. In the commercial data, we used the gross payments variable in the MarketScan data (PAY), which is the total amount paid to a provider for a service after applying discounts and before applying coordination of benefits and patient out-of-pocket. Though discounts are accounted for, it is unclear whether all types of discounts (such as rebates, which are often paid after point of sale) are included, and this also does not account for additional discounting and manufacturer incentives at the provider level. Thus, we observed a tempered price trend in the commercial sector, as we are not observing the true prices being paid.

Lastly, this study included only provider-administered biologics and the findings may differ for pharmacy biologics.

Future Research

Future research should explore the reason behind the insurance sector and drug-group market differences more explicitly. For the drugs included in this analysis, they are typically not on defined formularies through the pharmacy benefit but rather have associated contracts, policies, and reimbursement through the medical benefit. Thus, understanding market dynamics from the payer perspective could help identify some of the differences or predictors of market behavior. Expanding this analysis to the pharmacy benefit reference products and biosimilars is also important, as it is complicated further by Pharmacy Benefit Manager (PBM) involvement and lack of price transparency. Ultimately, policy initiatives should seek to reduce barriers to competition to promote biosimilar sustainability, such as changing reimbursement structure, improving transparency around discounts and rebates, reducing patent litigation, and overall incentivizing uptake of biosimilars, which typically results in savings.

Conclusion

This study highlights the substantial differences between biologics markets in trends in market share and price decline. These differences are present between product markets, as well as within product markets between the Medicare and commercial insurance sectors. With these differences in mind, it is difficult to draw conclusions about biologics markets generally, indicating uncertainty when it comes to predicting how a given market might behave in the future. This uncertainty may lead to hesitation from biosimilar manufacturers to enter and remain in the market, which can threaten the sustainability of biosimilar markets and therefore savings to payers and patients due to biosimilar competition.

CHAPTER 2. PATIENT OUT-OF-POCKET COSTS DUE TO RHEUMATOLOGY BIOSIMILAR COMPETITION

Abstract

Background

Despite demonstrated savings from biosimilars, evidence examining savings experienced by patients is mixed, especially in the commercially insured population. Reference product prices typically decrease after biosimilars enter the market, so documented savings from existing studies cannot causally conclude that biosimilar competition itself has led to overall savings biologic group savings for both reference products and biosimilars as prices come down.

Objective

The objective of this study is to assess the impact of biosimilar competition on patient out-of-pocket costs for rheumatology biologics.

Methods

We conducted a Callaway & Sant'Anna difference-in-differences analysis of patient OOP before and after biosimilar competition. We included infliximab, rituximab, and adalimumab as the drug groups of interest, as they are the rheumatology biologics with biosimilars available. The exposure in the analysis was biosimilar competition, and the outcome was biologic-related OOP costs.

Results

Overall, we observed significant patient OOP savings due to biosimilar competition, with an average annual savings of over $1,000 in the infliximab and rituximab groups during the study period. When assessing treatment effect by duration of exposure, we observed increasing savings over time, the longer biosimilars were available. In the adalimumab group, there was an increase

in patient OOP in the year prior to biosimilar availability, which may reflect price increases in anticipation of competition. There was minimal savings in the adalimumab group upon biosimilar entry, and no savings when accounting for one year of anticipatory effect, which here would represent anticipatory price increases.

Conclusions

Biosimilar competition resulted in decreased OOP costs in patients using infliximab and rituximab biologics, using similar biologics without biosimilars available as a control group. The results indicate that the availability of infliximab and rituximab biosimilars has led to significant savings for patients, with savings increasing more the longer biosimilars remain on the market. Because of these demonstrated savings, it is important that policies incentivize development of biosimilars and support the long-term availability of biosimilars to preserve and increase savings for patients.

Introduction

Biologic drugs account for a large and growing share of U.S. healthcare spending, representing approximately 45% of total drug expenditures ($324 billion) in 2023.[6] Managing these costs is of high priority for both public and commercial payers. The Biologics Price Competition and Innovation Act (BPCIA) of 2010 established an abbreviated pathway for the approval of biosimilars, which are highly similar with no clinically meaningful differences from their reference products, in order to promote competition and reduce costs.[17] Adoption of biosimilars has varied across therapeutic classes and payers due to differences in benefit design, rebates and discounts, provider and patient preferences, and misaligned incentives.[5,44] However, biosimilars have still produced substantial savings for payers and health systems to date, with significant potential for additional savings with increased competition.[2,5]

Evidence shows reductions in total spending after biosimilar entry, particularly in Medicare markets, whereas findings in commercial markets are less consistent due to differences in plan design, contracting, and limited data transparency.[45] While payer and health system savings are important, they do not necessarily translate to savings for patients as plan structures (deductibles, copayments, coinsurance, etc.) determine how savings are passed through to patients. Patient out-of-pocket (OOP) costs play a critical role in treatment access, affordability, and adherence, which are essential to realizing therapeutic benefit.[46]

Despite demonstrated savings from biosimilars for health systems and payers, evidence on whether biosimilar competition reduces patient OOP costs remains mixed, especially in the commercial population. Feng et al. examined the association between biosimilar competition and OOP costs in a commercial population using a two-part model, and showed that competition is not consistently associated with lower OOP costs.[9] Mouslim et al. studied filgrastim in a commercial

population between 2015-2017, and found reductions in claims payments but only slight changes in OOP.[10] Wang et al. found that pegfilgrastim OOP per-cycle costs were lower for those on biosimilars, but no difference in health plan and total costs in a commercial population.[11] Another study by Feng et al. studied infliximab specifically, and observed that average non-zero OOP costs increased after biosimilar competition.[8]

However, these studies generally compared biosimilar-related OOP to reference product-related OOP, which does not account for what would have happened to reference product prices in the absence of biosimilar competition (counterfactual price trends). Because reference product prices typically decline after biosimilars enter the market, these comparisons can demonstrate biosimilar savings relative to the reference product but cannot establish whether biosimilar competition itself led to lower overall OOP costs across the full biologic group (both biosimilars and reference products).

The objective of this study is to estimate the effect of biosimilar competition on patient OOP costs for rheumatology biologics, comparing observed OOP after biosimilar entry with predicted costs had no biosimilar been available. We do so by using comparable biologics without biosimilar competition as controls and estimate effects for both biologic-specific OOP and total annual OOP.

Methods

We conducted a difference-in-differences analysis of patient OOP before and after biosimilar competition using the methodology described by Callaway & Sant'Anna.[47] We included infliximab, rituximab, and adalimumab as the drug groups of interest, as they are the rheumatology biologics with biosimilars available. The exposure in the analysis was biosimilar competition (availability of biosimilars), and the outcome was biologic-related OOP costs (i.e. the amount the

patient spent in a given year on claims for these biologics). OOP was the sum of the amount paid toward the deductible, coinsurance, and copay.

Identification of Controls

We identified drugs to be included in the control group by reviewing clinical guidelines to identify biologics with similar mechanisms of action recommended for the FDA-approved indications held by the drugs of interest. We then confirmed FDA approval and approval dates of each drug based on their Prescribing Information. The included control drugs and their approval dates are shown in Table 2-1, and the full list of intervention and control drugs, their HCPCS and NDC identifiers, and FDA-approved indications are included in the Supplemental Appendix, Sections B1 and B2.

Table 2-1. Biologics Included in Control Group

Control Biologic Drugs	Approval
Actemra (tocilizumab)	Q1 2010
Arcalyst (rilonacept)	Q1 2008
Bimzelx (bimekizumab)	Q4 2023*
Cimzia (certolizumab pegol)	Q2 2008
Cozentyx (secukinumab)	Q1 2015
Enbrel (etanercept)	Q4 1998
Entyvio (vedolizumab)	Q2 2014
Ilaris (canakinumab)	Q2 2009
Kevzara (sarilumab)	Q2 2017
Kineret (anakinra)	Q4 2001
Orencia (abatacept)	Q4 2005
Siliq (brodalumab)	Q1 2017
Simponi (golimumab)	Q2 2009
Skyrizi (risankizumab)	Q2 2019
Stelara (ustekinumab)	Q3 2009
Tysabri (natalizumab)	Q4 2004
Taltz (ixekizumab)	Q1 2016
Tremfya (guselkumab)	Q3 2017

*bimekizumab was included in the control group, however was only approved at the end of the study period. There were no claims found for bimekizumab in the analysis.

Data Source

We used claims from the Merative™ MarketScan® Commercial Database from January 1, 2011 through December 31st, 2023. Claims associated with the drugs of interest were identified using the CMS Drug Pricing ASP and Crosswalk Files to as a source of HCPCS and NDC codes for each quarter plus any additional NDC codes identified in Merative™ Micromedex® RED BOOK® Online (both active and de-activated NDC codes).[12,14] HCPCS codes were used to identify outpatient and inpatient claims, and NDC codes were used to identify pharmacy claims. A table detailing the HCPCS and NDC codes used for each drug are included in the Supplementary Appendix, Section A2.

Some claims in the MarketScan data contain negative amounts that reflect adjustments to correct a claim reversal or payment error. These are largely resolved in the outpatient and pharmacy datasets and combined into one line; however, they are not resolved in the inpatient services dataset and there are still some adjustment records remaining in all three. To avoid inflating OOP by simply removing all negative values, we summed financial variables for each patient and drug on a given service date and kept all positive values. Then, the financial variables for all included claims were summed by patient for each year to get the annual OOP due to the biologic drug and the total annual OOP.

Patient Inclusion Criteria

Patients were included if they had two drug claims for the same qualifying drug in each year of inclusion and had continuous enrollment for the whole year. Patients were excluded if they appeared in two drug groups over the course of the study period. Patients were not required to be included or enrolled in more than one year at a time. Patient characteristics of age, sex, and plan

type in each year were examined to identify characteristics that may differ between treatment and control groups.

Statistical Analysis

There is substantial evidence that the prices of reference products and biosimilars have evolved differently in different biologic groups post-biosimilar entry.[2,18] The patient OOP for physician-administered biologics is often a percentage of the price (coinsurance) and thus we can expect that the effect on patient OOP will likely differ between biologic groups. This can be described as a heterogeneous treatment effect. Additionally, biologic groups are exposed to biosimilar competition at different times rather than a single point. Traditional two-way fixed-effects difference-in-differences analysis is subject to significant bias in the presence of treatment effect heterogeneity and variation in treatment timing. Instead, we used the Callaway & Sant'Anna methodology for difference-in-differences analysis, which is valid in this context to estimate a group-time average treatment effect without contamination from other periods.[47] Group-time average treatment effects can be aggregated to estimate group-specific effects to examine each biologic group individual, as well as into an event study to summarize treatment effect by length of exposure, which in this case is duration of biosimilar availability. The simple aggregated treatment effect can be calculated as well, but this is over-weights earlier treated groups and is difficult to generalize.[48]

For the primary analysis, we used the "never-treated" (never exposed) control biologics, meaning that the data for the intervention groups pre-intervention was not used in the control group ("not-yet-treated"). We conducted a robustness check using not-yet-treated as the control group. We allowed an unbalanced panel due to changes in treatment over time and the unlikelihood of patients remaining on a given medication for the whole study period. Forcing a balanced panel resulted in

significant decrease in sample size. In that sense, the analysis was akin to a repeated cross-sectional analysis but treating it as an unbalanced panel still allows for controlling for individual effects. As a robustness check, we also ran the analysis as a repeated cross-sectional study.

Initial data cleaning and claim inclusion/exclusion was conducted using SAS version 9.4. Subsequent data manipulation and analyses were conducted using R version 4.5.0. The analysis relied on de-identified claims data and met criteria for non-human subjects research, so IRB approval was not required.

Results

Patient Population

After identifying claims based on the inclusion and exclusion criteria, the sample size was 572,206 patient-years in the intervention group (infliximab, rituximab, adalimumab) and 413,464 patient-years in the control group. This translated to 270,352 individual patients in the intervention group and 196,007 patients in the control group. Table 2-2 shows the patient characteristics in the treatment and control group. Details of the sample size at each inclusion and exclusion step and patient characteristics in the treatment and control group in each year are included in the Supplemental Appendix, Section B3.

Table 2-2. Patient Characteristics

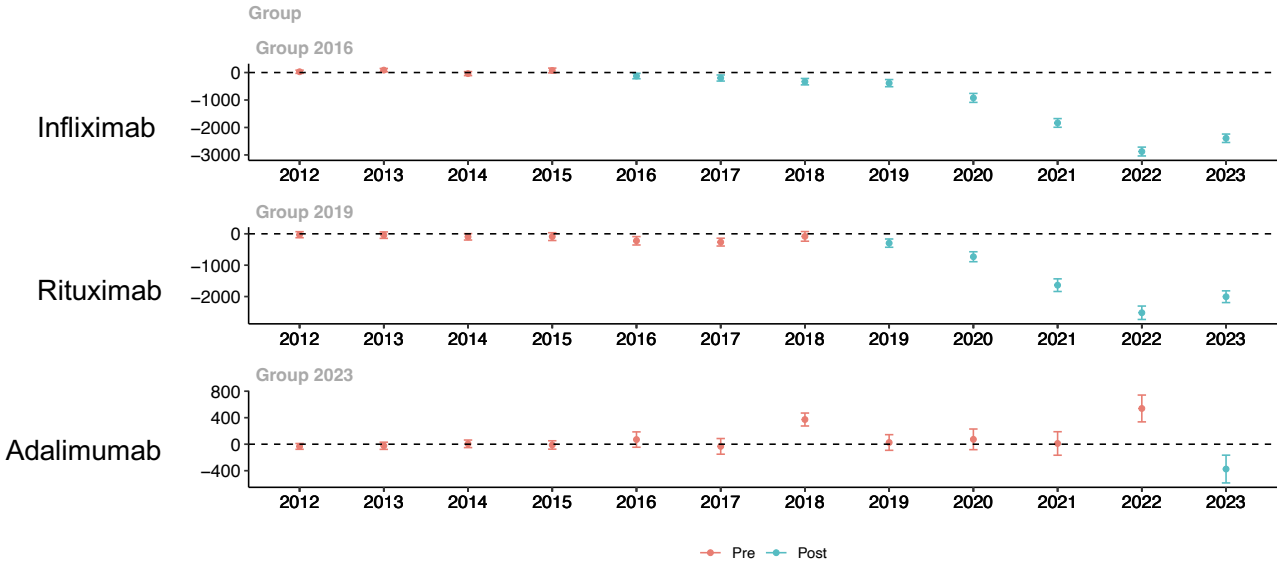
	Intervention	Control
N (patient-years)	572,206	413,464
Age, Mean (SD)	44.1 (14.2)	46.9 (12.4)
Age, Median [min, max]	47.0 [0, 64.0]	49.0 [0, 64.0]
Female, n (%)	308,905 (54.0%)	253,662 (61.4%)
Plan Types, n (%)		
PPO	323,301 (56.5%)	230,682 (55.8%)
EPO	6,874 (1.2%)	4,538 (1.1%)
HDHP	43,644 (7.6%)	31,857 (7.7%)
HMO	64,772 (11.3%)	46,770 (11.3%)
Multiple	4,767 (0.8%)	3,597 (0.9%)
Other	128,858 (22.5%)	96,020 (23.2%)

Key: PPO – Preferred Provider Organization; EPO – Exclusive Provider Organization; HDHP – High-Deductible Health Plan; HMO – Health Maintenance Organization; Multiple – patients had more than one different plan types documented across their claims in a given year. Other includes: "Basic/Major Medical Plan", "Comprehensive Plan", Non-Capitated Point-of-Service Plan, Capitated or Partially Capitated Point-of-Service Plan, and Consumer-Driven Health Plan (CDHP).

Group-Time Average Treatment Effect

The group-time average treatment effect reports the average treatment effect for each group at each time point, as shown in Figure 2-1. In the infliximab and rituximab groups, the pre-period estimates show no evidence of systematic differences between treatment and control groups. In the adalimumab group, there is a significant deviation from zero in the final pre-period (event time = -1). As a robustness check, we conducted the analysis accounting for one year of anticipation (see Supplemental Appendix, Section B6), which resulted in an increase in patient OOP in the adalimumab group in the one post-period. Given that there is only one year (2023) of data available in the post-period, it is difficult to draw conclusions for the adalimumab group. In the infliximab and rituximab groups, there is a clear downward trend in patient biologic OOP in the post-period that indicates savings due to biosimilar competition. The full result tables are included in the Supplemental Appendix, Section B4.

Figure 2-1. Group-Time Average Treatment Effect, Biologic OOP



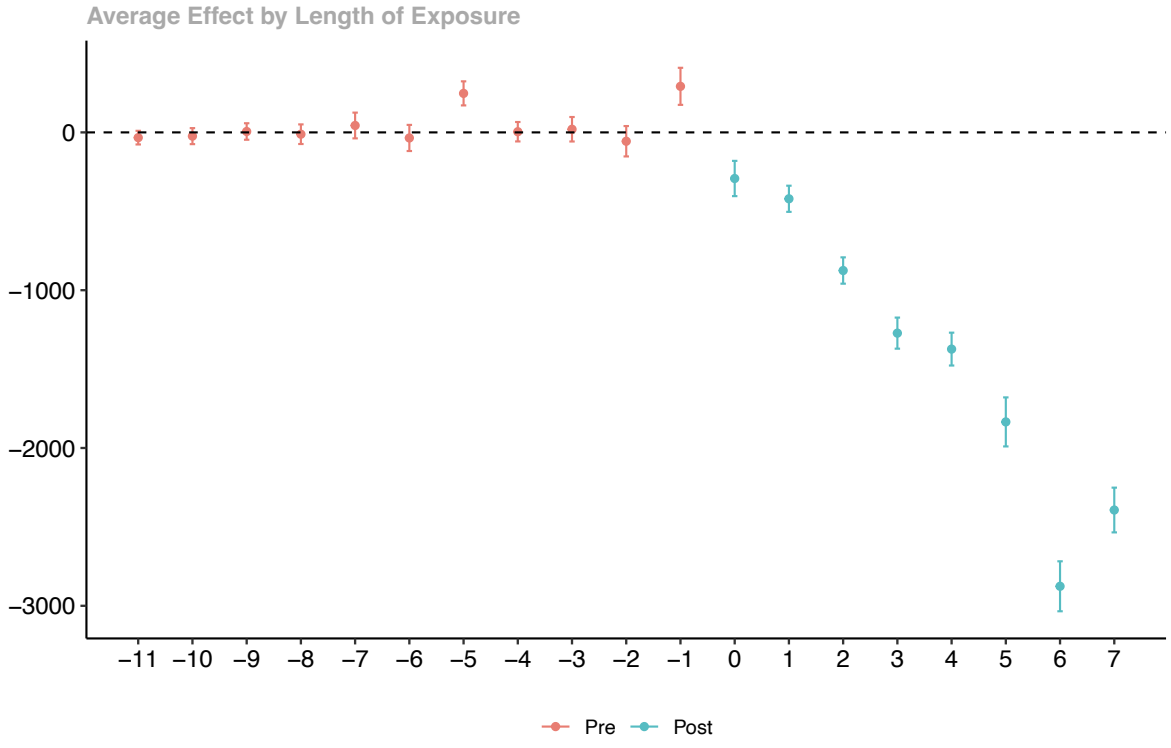
We also conducted this analysis using total annual OOP. The results were very similar to the biologic OOP, indicating that savings on total annual OOP was due to biologic-related savings rather than other healthcare or drug costs that changed over time, and patients still experienced savings despite plan designs with an OOP maximum. The results for total annual OOP are included in the Supplemental Appendix, Section B5.

Average Effect by Length of Exposure (Event Study)

We then used the results to generate an event study to assess the average effect by length of exposure. As shown in Figure 2-2, patient biologic OOP decreases (savings increase) over time the longer a biologic group is exposed to competition. Because a large proportion of patients are in the adalimumab group, the event study also shows a significant deviation from zero in the final pre-period (event time = -1). Despite this, there is a very clear downward trend in patient OOP in the post-period, indicating that longer exposure to biosimilar competition leads to increased savings for patients. The full result tables are included in the Supplemental Appendix, Section B4.

To support this conclusion, we formally assessed pre-trends by computing the mean of all pre-treatment ATT estimates. Including all pre-periods, the average ATT was statistically different from zero due to the outlier at event time = –1. Excluding that period, the mean pre-treatment ATT was 16.12 (p = 0.506), consistent with no systematic differences prior to treatment. Previous research indicates that the final pre-period can cause rejections of the parallel trends assumption in staggered treatment time designs such as this one.[49,50] A precision-weighted average, which gives more weight to more precisely estimated pre-period effects, yielded a nearly identical conclusion (5.73, p = 0.402).

Figure 2-2. Average Effect by Length of Exposure, Biologic OOP

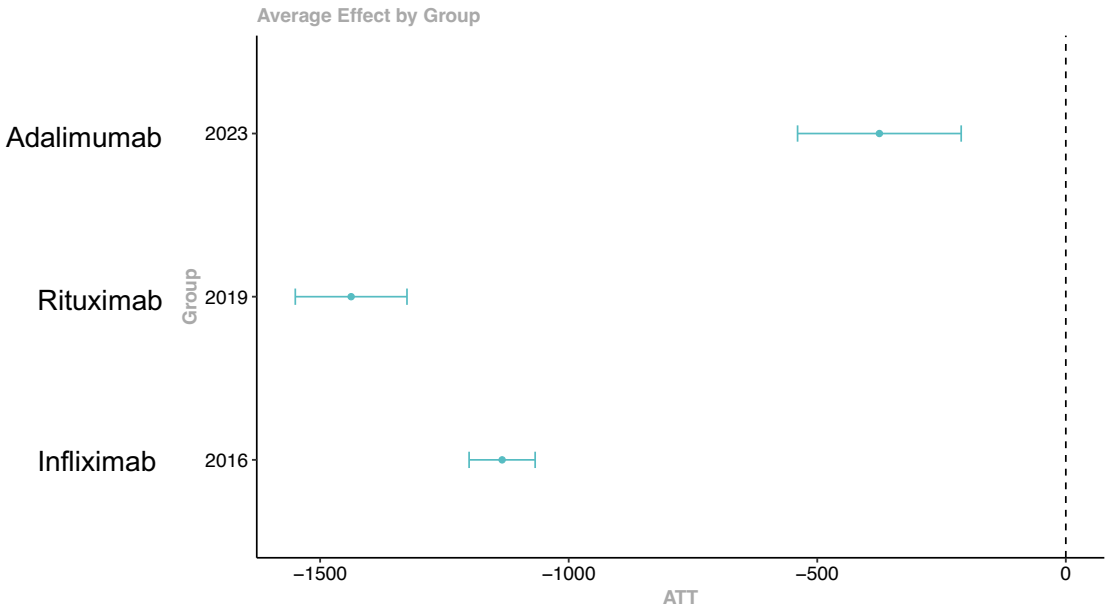


Again, the results for total annual OOP were very similar to the biologic OOP results and are included in the Supplemental Appendix, Section B5.

Group-Time Average Treatment Effect, By Group

We also calculated average treatment effect by group, shown in Figure 2-3. Given the downward trend in OOP by duration of exposure, the average savings in the rituximab group were actually higher than infliximab, despite infliximab having been exposed to biosimilar competition for three years longer. We observed an average OOP difference of -$1,133.90 (95% CI -$1,200.35, -$1,067.45) in the infliximab group, -$1,437.63 (95% CI -$1,549.98, -$1,325.28) in the rituximab group, and -$375.01 (95% CI -$539.57, -$210.45) in the adalimumab group. However, when accounting for one year of anticipation, the result in the adalimumab group became $164.30 (95% CI $4.98, $323.63).

Figure 2-3. Average Effect by Group, Biologic OOP



Simple Aggregated Average Treatment Effect

The simple aggregated results tend to overweight earlier treated groups and aggregates across the whole time period, which varies depending on the group. Thus, we do not report the simple aggregated results as they overweight infliximab, but we did use the simple aggregated results in our robustness checks as a means of comparing results in different scenarios. These are reported

in the Supplemental Appendix, Section B6. No robustness checks, including treating the data as repeated cross-sections instead of an unbalanced panel, gave results significantly different than the primary analysis, giving us confidence in these estimates.

Discussion

We studied the impact of biosimilar competition on patient OOP for rheumatology biologics infliximab, rituximab, and adalimumab, using comparable biologics that do not have a biosimilar available as a control group. Overall, we observed significant savings due to biosimilar competition, with an average annual savings of over $1,000 in the infliximab and rituximab groups during the study period. When assessing treatment effect by duration of exposure, we observed increasing savings over time, the longer biosimilars were available. This highlights that the availability of infliximab and rituximab biosimilars has led to significant savings for patients, with more savings the longer biosimilars are on the market. In the adalimumab group, there was an increase in patient OOP in the year prior to biosimilar availability. When looking at patient OOP in both the control group and intervention groups, there is a clear increase in OOP in 2022 in both adalimumab and the control group (see Supplemental Appendix, Section B6). This increase in 2022 may be due to manufacturers increasing prices prior to the implementation of the Inflation Reduction Act, which requires manufacturers to pay rebates to the federal government for any price increases greater than the rate of inflation beginning October 1, 2022.[51] The increase in adalimumab OOP is higher than the increase in the control group, leading to the increase in patient OOP in the adalimumab group compared to the control group in the year prior to biosimilar availability, which may be due to manufacturer pricing strategy or additional anticipatory price increase on top of the pre-IRA increase. There was minimal savings in the adalimumab group upon biosimilar entry, and no savings when accounting for one year of anticipation. However, there is

still potential for biosimilars to lead to savings in this market, which can only be assessed when more data is available.

The effect of biosimilar competition on patient OOP was very similar when looking solely at biologic-related OOP and when looking at total annual OOP, which indicates that biologic-related savings are not being absorbed by other healthcare costs but are truly being experienced by patients with their biologic claims. However, we do not have information about the amount that premiums may have increased during this time period for these commercial plans.

Prior research studying patient OOP and biosimilar competition has primarily focused on comparing OOP between biosimilars and reference products.[8–11] Studies forecasting the savings due to biosimilars use the prices of reference products as the scenario in the absence of biosimilars. However, these studies do not use a control group to model what would likely have occurred to OOP during the same time period in the absence of biosimilar competition and thus cannot attribute differences in OOP to biosimilar competition. In our study, the difference-in-differences design allows for drawing causal conclusions about the effects of biosimilar competition, and we show that in the infliximab and rituximab markets, biosimilar competition does conclusively lead to lower patient OOP.

The findings of this study have significant implications for biosimilar-related policy because we show that patients are experiencing savings compared to what they otherwise might be paying. Our results add to the growing body of research that indicates the savings related to biosimilar availability. This highlights the need for policy that incentivizes biosimilar development, removes approval barriers (as the FDA has recently proposed), and supports the sustainability of biosimilars markets to preserve and encourage biosimilar availability to enable continued savings. However, there is significant variation in the behavior of biologic markets in general and especially after

biosimilar entry. Thus, the conclusions of this study are only directly applicable to infliximab and rituximab, but the difference-in-differences methodology using comparable biologics without biosimilars available as a control group should be considered for future analysis of the savings for patients due to biosimilar competition.

This study is not without limitations. Infliximab and rituximab are both primarily medical benefit drugs, and their patient OOP payments are often based on a percentage of the allowable amount or price. Drugs that are administered subcutaneously and are more frequently on the pharmacy benefit (such as adalimumab) may differ in their OOP trends due to formulary structures and PBM involvement. However, in the Medicare Part D benefit, there has been somewhat of a shift toward the coinsurance model in pharmacy benefit drugs – so while this isn't directly generalizable to the structure of most pharmacy benefit drugs, it is relevant for coinsurance-based OOP.[52] Additionally, we do not have information about premiums, and thus overall patient OOP may be increasing if premium increases are outpacing the savings.

As discussed above, these results are not generalizable to all biologic and biosimilar markets due to significant variation in market dynamics. These results are also not generalizable to Medicare, as this data only includes the commercial population.

Conclusion

Biosimilar competition resulted in decreased patient out of pocket costs in patients using infliximab and rituximab biologics, using similar biologics without biosimilars available as a control group. This study highlights the importance of policies that incentivize development of biosimilars and support the long-term availability of biosimilars to preserve and increase savings for patients.

CONCLUSION

Summary of Findings

To contribute to the body of evidence surrounding biologics and their biosimilars and the importance of policies and incentives to create a more robust biosimilars market long-term, we sought to characterize biologic markets in terms of price and market share and estimate the impact of biosimilar competition on patient out-of-pocket costs.

In the first study, we examined the price decline in biosimilars versus reference products and market share of reference products after biosimilar entry. We found that reference product market share declined in most markets after biosimilar entry, but the rate and pattern of this decline varied substantially across drug groups and between sectors. Price dynamics were also heterogeneous, with biosimilar prices declining more steeply than reference products in the Medicare but not in the commercial sector. Price trends also differed markedly across biologic groups. These findings highlight the heterogeneity of competition in U.S. biosimilar markets and the limitations of drawing generalized conclusions about the effects of biosimilar entry or how a given market may behave in the future.

In the second study, we examined the impact of biosimilar competition on patient OOP costs for rheumatology biologics infliximab, rituximab, and adalimumab, using comparable biologics with no biosimilar as a control group. Overall, we observed statistically significant savings due to biosimilar competition, with an average savings of over $1,000 in the infliximab and rituximab groups during the study period – eight years post-biosimilar entry for infliximab and five years post-biosimilar entry for rituximab. When assessing treatment effect by duration of exposure, we observed increasing savings over time, the longer biosimilars were available. This highlights that

the availability of infliximab and rituximab biosimilars led to significant savings for patients, with more savings the longer biosimilars are on the market. There was minimal savings in the adalimumab group upon biosimilar entry, and no savings when accounting for one year of anticipation. However, there is still potential for biosimilars to lead to savings in this market, which can only be assessed when more data is available.

Together, these studies provide context for the importance of policies that incentivize development of biosimilars and support the long-term availability of biosimilars to preserve and increase savings for patients and the health care system.

Implications for Policy and Research

The findings of this study have significant implications for biosimilar-related policy, particularly highlighting the need for policies that incentivize biosimilar uptake and improve the stability and predictability of the markets to preserve long-term savings. As they are, competition effects are highly variable both in terms of price and market share, which could contribute to manufacturer hesitancy to develop biosimilars. This research also adds to the growing body of literature that indicates the substantial savings related to biosimilar availability, specifically showing that patients are experiencing savings compared to what they otherwise might be paying in the absence of biosimilar competition. Further research can be conducted using the methodology we used to assess patient out-of-pocket costs in additional biologics markets to calculate savings due to biosimilar competition other than just the savings incurred from biosimilar utilization.

These studies highlight the need for policies that incentivize biosimilar development, remove barriers to competition such as patent litigation and separate reimbursement rates, and enhances

competition to support the sustainability of biosimilars markets to enable continued savings and access for patients.

REFERENCES

1. Monge A, Thai L. *Issue Brief: Competition in the U.S. Therapeutic Biologics Market*. ASPE Office of Science and Data Policy; 2025.

2. IQVIA. *Biosimilars in the United States 2023–2027*. IQVIA Institute for Human Data Science; 2023. https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/biosimilars-in-the-united-states-2023-2027

3. Roth JA, Dayer VW, Jofre-Bonet M, McGuire A, Sullivan SD. Defining a Framework for Sustainable Global Biosimilars Markets Using Findings from a Targeted Literature Review. *BioDrugs*. Published online February 26, 2025. doi:10.1007/s40259-025-00710-8

4. IQVIA. *Long-Term Market Sustainability for Infused Biosimilars in the U.S.: Foundational Analytics on Emerging Risks to Sustainability*. IQVIA Institute for Human Data Science; 2024. https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/long-term-market-sustainability-for-infused-biosimilars-in-the-us

5. Association for Accessible Medicines. *The U.S. Generic & Biosimilar Medicines Savings Report 2025*.; 2025. https://accessiblemeds.org/wp-content/uploads/2025/09/AAM-2025-Generic-Biosimilar-Medicines-Savings-Report-WEB.pdf

6. IQVIA. *Assessing the Biosimilar Void in the US*. IQVIA Institute for Human Data Science; 2025. https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/assessing-the-biosimilar-void-in-the-us/iqvia-institute-biosimilar-void-us-report-02-25-forweb.pdf

7. Mulcahy A, Buttorff C. Projected US Savings from Biosimilars, 2021-2025. *Am J Manag Care*. 2022;28(7):329-335. doi:10.37765/ajmc.2022.88809

8. Feng K, Kesselheim AS, Russo M, Rome BN. Patient Out-of-Pocket Costs Following the Availability of Biosimilar Versions of Infliximab. *Clin Pharmacol Ther*. 2023;113(1):90-97. doi:10.1002/cpt.2763

9. Feng K, Russo M, Maini L, Kesselheim AS, Rome BN. Patient Out-of-Pocket Costs for Biologic Drugs After Biosimilar Competition. *JAMA Health Forum*. 2024;5(3):e235429. doi:10.1001/jamahealthforum.2023.5429

10. Mouslim MC, Trujillo AJ, Alexander GC, Segal JB. Association Between Filgrastim Biosimilar Availability and Changes in Claim Payments and Patient Out-of-Pocket Costs for Biologic Filgrastim Products. *Value Health*. 2020;23(12):1599-1605. doi:10.1016/j.jval.2020.06.014

11. Wang CY, Park H, Heldermon CD, Vouri SM, Brown JD. Patient out-of-pocket and payer costs for pegfilgrastim originator vs biosimilars as primary prophylaxis of febrile neutropenia in the first cycle among a commercially insured population. *J Manag Care Spec Pharm*. 2022;28(7):795-802. doi:10.18553/jmcp.2022.28.7.795

12. ASP Pricing Files | CMS. CMS.gov. July 9, 2025. Accessed February 11, 2025. https://www.cms.gov/medicare/payment/part-b-drugs/asp-pricing-files

13. CMS. Limited Data Set (LDS) Files. Published online 2025. https://www.cms.gov/data-research/files-for-order/data-disclosures-and-data-use-agreements-duas/limited-data-set-lds

14. Merative Micromedex. RED BOOK® Online. Published online 2025. Accessed February 11, 2025. http://www.micromedexsolutions.com

15. U.S. Bureau of Labor Statistics. Consumer Price Index (CPI) Databases. Published online 2025. Accessed June 1, 2025. https://www.bls.gov/cpi/data.htm

16. Chen AJ, Kaiser KM, Gascue L, Manetas MA, Van Nuys K. Cancer Drug Trastuzumab And Its Biosimilars Compete On Price For Market Share. *Health Aff (Millwood)*. 2023;42(6):779-784. doi:10.1377/hlthaff.2022.01448

17. Center for Drug Evaluation and Research. Commemorating the 15th Anniversary of the Biologics Price Competition and Innovation Act. FDA. March 26, 2025. Accessed October 15, 2025. https://www.fda.gov/drugs/cder-conversations/commemorating-15th-anniversary-biologics-price-competition-and-innovation-act

18. Jofre-Bonet M, McGuire A, Dayer V, Roth JA, Sullivan SD. The Price Effects of Biosimilars in the United States. *Value Health*. Published online March 4, 2025. doi:10.1016/j.jval.2025.02.008

19. Johnson M, Nguyen NX, Sheingold SH. *Medicare Part B Enrollee Use and Spending on Biosimilars, 2018-2023*. ASPE Office of Health Policy; 2025.

20. Medical Benefit vs. Pharmacy Benefit. DocStation. August 23, 2022. Accessed October 23, 2025. https://docstation.co/medical-benefit-vs-pharmacy-benefit/

21. Prescription drugs (outpatient). Medicare.gov. Accessed October 23, 2025. https://www.medicare.gov/coverage/prescription-drugs-outpatient

22. What's Medicare Drug Coverage (Part D)? Medicare.gov. Accessed October 23, 2025. https://www.medicare.gov/health-drug-plans/part-d

23. National Archives. 42 CFR 414.804 -- Basis of payment. Code of Federal Regulations. January 3, 2017. Accessed August 5, 2024. https://www.ecfr.gov/current/title-42/part-414/section-414.804

24. Federal Register. Medicare Program; Manufacturer Submission of Manufacturer's Average Sales Price (ASP) Data for Medicare Part B Drugs and Biologicals. Federal Register. April 6, 2004. Accessed August 2, 2024. https://www.federalregister.gov/documents/2004/04/06/04-7715/medicare-program-manufacturer-submission-of-manufacturers-average-sales-price-asp-data-for-medicare

25. CMS. Average Sales Price (ASP) Quarterly Publication Process FAQs. Published online January 17, 2025. Accessed May 28, 2024. https://www.cms.gov/files/document/frequently-asked-questions-faqs-asp-data-collection.pdf

26. Rome BN, Sarpatwari A. Promoting Biosimilar Competition by Revising Medicare Reimbursement Rules. *JAMA Netw Open*. 2021;4(11):e2134463. doi:10.1001/jamanetworkopen.2021.34463

27. Association for Accessible Medicines Biosimilars Council. How to Solve the Buy-and-Bill Biosimilar Pricing Puzzle? Published online 2025. https://biosimilarscouncil.org/wp-content/uploads/2025/08/AAM-BC-How-to-Solve-the-Buy-and-Bill-Biosimilar-Pricing-Puzzle.pdf

28. Hansen RN, Roth JA, Dayer VW, Sullivan SD. Reforming Average Sales Price-Based Reimbursement For Infused Biosimilars. Health Affairs Forefront. November 3, 2025. Accessed November 3, 2025. https://www.healthaffairs.org/do/10.1377/forefront.20251030.152901/full/

29. Center for Drug Evaluation and Research. *Report | Drug Shortages: Root Causes and Potential Solutions*. FDA; 2020. Accessed June 12, 2024. https://www.fda.gov/drugs/drug-shortages/report-drug-shortages-root-causes-and-potential-solutions

30. Dave CV, Pawar A, Fox ER, Brill G, Kesselheim AS. Predictors of Drug Shortages and Association with Generic Drug Prices: A Retrospective Cohort Study. *Value Health*. 2018;21(11):1286-1290. doi:10.1016/j.jval.2018.04.1826

31. Carl DL, Laube Y, Serra-Burriel M, Naci H, Ludwig WD, Vokinger KN. Comparison of Uptake and Prices of Biosimilars in the US, Germany, and Switzerland. *JAMA Netw Open*. 2022;5(12):e2244670. doi:10.1001/jamanetworkopen.2022.44670

32. McGeeney JD, Sertkaya A, McCormick SA, et al. Measuring the First Mover Advantage in US Biosimilar Markets. *Value Health*. Published online July 2025:S1098301525024787. doi:10.1016/j.jval.2025.07.011

33. Office of the Inspector General. Biosimilar Cost and Use Trends in Medicare Part B. Published online 2021.

34. Stern AD, Chen JL, Ouellet M, et al. Biosimilars And Follow-On Products In The United States: Adoption, Prices, And Users. *Health Aff (Millwood)*. 2021;40(6):989-999. doi:10.1377/hlthaff.2020.02239

35. The Center for Biosimilars. Biosimilar Approvals. Center for Biosimilars. January 7, 2025. Accessed October 16, 2025. https://www.centerforbiosimilars.com/biosimilar-approvals

36. Chen AJ, Gascue L, Ribero R, Van Nuys K. Uptake of Infliximab Biosimilars Among the Medicare Population. *JAMA Intern Med*. 2020;180(9):1255. doi:10.1001/jamainternmed.2020.3188

37. Chen A, Ribero R. Provider differences in biosimilar uptake in the filgrastim market. *Am J Manag Care*. 2020;26(5):208-213. doi:10.37765/ajmc.2020.42786

38. Hussaini SMQ, Gupta A, Anderson KE, Ballreich JM, Nicholas LH, Alexander GC. Utilization of Filgrastim and Infliximab Biosimilar Products in Medicare Part D, 2015-2019. *JAMA Netw Open*. 2022;5(3):e221117. doi:10.1001/jamanetworkopen.2022.1117

39. Cohen JP, Felix AE, Riggs K, Gupta A. Barriers to Market Uptake of Biosimilars in the US. *Generics Biosimilars Initiat J*. 2014;3(3):108-115. doi:10.5639/gabij.2014.0303.028

40. Leber MB. Optimizing Use and Addressing Challenges to Uptake of Biosimilars. *Am J Manag Care*. 2018;24(21 Suppl):S457-S461.

41. Tony Hagen. Sandoz Is 0-3 in Enbrel Patent Case. Center for Biosimilars. May 17, 2021. Accessed October 10, 2025. https://www.centerforbiosimilars.com/view/sandoz-is-0-3-in-enbrel-patent-case

42. Jacob Bell. Viatris sells off biosimilars business in $3.3B deal | BioPharma Dive. BioPharmaDive. February 28, 2022. Accessed October 10, 2025. https://www.biopharmadive.com/news/biocon-viatris-biosimilars-deal/619514/

43. Mehr S. Part B Biosimilar Sustainability Also in Question | BR&R. March 7, 2024. Accessed March 15, 2024. https://biosimilarsrr.com/2024/03/07/part-b-biosimilar-sustainability-also-in-question/

44. Sullivan SD, Humphreys SZ, Fox D, et al. Stakeholder perspectives on the sustainability of the United States biosimilars market. *J Manag Care Spec Pharm*. Published online July 16, 2024:1-8. doi:10.18553/jmcp.2024.24104

45. Maxwell A. *Biosimilars Have Lowered Costs for Medicare Part B and Enrollees, but Opportunities for Substantial Spending Reductions Still Exist*. U.S. Department of Health and Human Services, Office of Inspector General; 2023. https://oig.hhs.gov/reports-and-publications/all-reports-and-publications/biosimilars-have-lowered-costs-for-medicare-part-b-and-enrollees-but-opportunities-for-substantial-spending-reductions-still-exist/

46. Fusco N, Sils B, Graff JS, Kistler K, Ruiz K. Cost-sharing and adherence, clinical outcomes, health care utilization, and costs: A systematic literature review. *J Manag Care Spec Pharm*. 2023;29(1):10.18553/jmcp.2022.21270. doi:10.18553/jmcp.2022.21270

47. Callaway B, Sant'Anna PHC. Difference-in-Differences with multiple time periods. *J Econom*. 2021;225(2):200-230. doi:10.1016/j.jeconom.2020.12.001

48. Callaway B, Sant'Anna PHC. Getting Started with the did Package. GitHub. September 10, 2024. Accessed September 27, 2024. https://bcallaway11.github.io/did/articles/did-basics.html

49. Roth J. Pretest with Caution: Event-Study Estimates after Testing for Parallel Trends. *Am Econ Rev Insights*. 2022;4(3):305-322. doi:10.1257/aeri.20210236

50. Bilinski A, Hatfield LA. Nothing to see here? Non-inferiority approaches to parallel trends and other model assumptions. *arXiv*. Preprint posted online January 17, 2020. doi:10.48550/arXiv.1805.03273

51. Arielle Bosworth, Steven Sheingold, Kenneth Finegold, Nancy De Lew, Benjamin D. Sommers. *Price Increases for Prescription Drugs, 2016-2022*. ASPE Office of Health Policy; 2022. Accessed November 5, 2025. https://aspe.hhs.gov/sites/default/files/documents/e9d5bb190056eb94483b774b53d512b4/price-tracking-brief.pdf

52. Erin Trish, Barbara Blaylock. *Shifting Cost-Sharing Burden to Beneficiaries in Medicare Part D*. USC Schaeffer; 2025. Accessed October 30, 2025. https://schaeffer.usc.edu/research/cost-sharing-burden-medicare-part-d/

53. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Care Res*. 2021;73(7):924-939. doi:10.1002/acr.24596

54. Ward MM, Deodhar A, Gensler LS, et al. 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. *Arthritis Rheumatol*. 2019;71(10):1599-1613. doi:10.1002/art.41042

55. Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2019;80(4):1029-1072. doi:10.1016/j.jaad.2018.11.057

56. Rubin DT, Ananthakrishnan AN, Siegel CA, Barnes EL, Long MD. ACG Clinical Guideline Update: Ulcerative Colitis in Adults. 2025;120.

57. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG Clinical Guideline: Management of Crohn's Disease in Adults. *Am J Gastroenterol*. 2018;113(4):481-517. doi:10.1038/ajg.2018.27

58. Humira (adalimumab) Prescribing Information. Published online February 2024. https://www.rxabbvie.com/pdf/humira.pdf

59. Remicade (infliximab) Prescribing Information. Published online February 2025. https://www.jnjlabels.com/package-insert/product-monograph/prescribing-information/REMICADE-pi.pdf

60. Rituxan (rituximab) Prescribing Information. Published online December 2021. https://www.gene.com/download/pdf/rituxan_prescribing.pdf

61. Orencia (abatacept) Prescribing Information. Published online May 2024. https://packageinserts.bms.com/pi/pi_orencia.pdf

62. Kineret (anakinra) Prescribing Information. Published online September 2024. https://kineretrxhcp.com/pdf/Full-Prescribing-Information-English.pdf

63. Bimzelx (bimekizumab) Prescribing Information. Published online November 2024. Accessed December 26, 2024. https://www.bimzelx.com/prescribing-information.pdf

64. Siliq (brodalumab) Prescribing Information. Published online August 2024. https://pi.bauschhealth.com/globalassets/BHC/PI/Siliq-pi.pdf

65. Ilaris (canakinumab) Prescribing Information. Published online November 2024. Accessed December 26, 2024. https://www.novartis.com/us-en/sites/novartis_us/files/ilaris.pdf

66. Cimzia (certolizumab pegol) Prescribing Information. Published online September 2024. https://www.cimzia.com/themes/custom/cimzia/docs/CIMZIA_full_prescribing_information.pdf

67. Enbrel (etanercept) Prescribing Information. Published online September 2024. https://www.pi.amgen.com/-/media/Project/Amgen/Repository/pi-amgen-com/Enbrel/enbrel_pi_CURNT.pdf

68. Simponi Aria (golimumab) Prescribing Information. Published online February 2021. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/SIMPONI+ARIA-pi.pdf

69. Simponi (golimumab) Prescribing Information. Published online October 2025. https://www.jnjlabels.com/package-insert/product-monograph/prescribing-information/SIMPONI-pi.pdf

70. Tremfya (guselkumab) Prescribing Information. Published online September 2025. https://www.jnjlabels.com/package-insert/product-monograph/prescribing-information/TREMFYA-pi.pdf

71. Taltz (ixekizumab) Prescribing Information. Published online August 2024. Accessed December 26, 2024. https://uspl.lilly.com/taltz/taltz.html#pi

72. Tysabri (natalizumab) Prescribing Information. Published online March 2025. https://www.tysabri.com/content/dam/commercial/tysabri/pat/en_us/pdf/tysabri_prescribing_information.pdf

73. Arcalyst (rilonacept) Prescribing Information. Published online May 2021. https://www.arcalysthcp.com/sites/default/files/2024-09/PI_IFU.pdf

74. Skyrizi (risankizumab) Prescribing Information. Published online September 2025. Accessed December 26, 2024. https://www.rxabbvie.com/pdf/skyrizi_pi.pdf

75. Kevzara (sarilumab) Prescribing Information. Published online May 2025. https://products.sanofi.us/Kevzara/Kevzara.pdf

76. Cosentyx (secukinumab) Prescribing Information. Published online October 2024. Accessed December 26, 2024. https://www.novartis.com/us-en/sites/novartis_us/files/cosentyx.pdf

77. Actemra (tocilizumab) Prescribing Information. Published online September 2024. https://www.gene.com/download/pdf/actemra_prescribing.pdf

78. Stelara (ustekinumab) Prescribing Information. Published online June 2025. https://www.jnjlabels.com/package-insert/product-monograph/prescribing-information/STELARA-pi.pdf

79. Entyvio (vedolizumab) Prescribing Information. Published online April 2024. https://content.takeda.com/?contenttype=PI&product=ENTY&language=ENG&country=USA&documentnumber=1

SUPPLEMENTAL APPENDICES

Appendix A: Chapter 1 Appendix

A1. Drug Identifiers

Table A 1. Included Drugs and Identifiers

Brand Name	Non-proprietary name	HCPCS	NDCs
Avastin	bevacizumab	J9035	71266-8005-01, 71266-8005-02, 50242-0060-01, 50242-0060-02, 50242-0060-10, 50242-0061-01, 50242-0061-10
Alymsys	bevacizumab-maly	Q5126	70121-1754-01, 70121-1754-07, 70121-1755-01, 70121-1755-07
Mvasi	bevacizumab-awwb	Q5107	55513-0207-01, 55513-0206-01
Vegzelma	bevacizumab-adcd	Q5129	72606-0012-01, 72606-0011-01
Zirabev	bevacizumab-bvzr	Q5118	00069-0315-01, 00069-0342-01
Epogen	epoetin-alfa (non-ESRD)	J0885	54569-3137-00, 55513-0283-10, 55513-0144-10, 55513-0144-01, 55513-0283-01, 55513-0267-01, 55513-0267-10, 55513-0148-01, 55513-0148-10, 55513-0126-01, 55513-0126-10, 55513-0478-10, 55513-0478-01, 55513-0823-01, 55513-0823-10
Retacrit	epoetin alfa-epbx (non-ESRD)	Q5106	00069-1309-01, 00069-1309-04, 00069-1309-10, 00069-1306-01, 00069-1306-10, 00069-1307-01, 00069-1307-10, 00069-1305-01, 00069-1305-10, 00069-1318-10, 00069-1318-01, 00069-1308-10, 00069-1308-01, 00069-1311-10, 00069-1311-01, 59353-0003-10, 59353-0003-01, 59353-0004-01, 59353-0004-10, 59353-0002-10, 59353-0002-01, 59353-0010-01, 59353-0220-10, 59353-0220-01, 59353-0010-10, 59353-0120-01, 59353-0120-10
Remicade	infliximab	J1745	57894-0160-01, 57894-0030-01
Avsola	infliximab-aqqx	Q5121	55513-0670-01
Inflectra	infliximab-dyyb	Q5103	00069-0809-01
Renflexis	infliximab-abda	Q5104	00006-4305-02, 78206-0162-01, 78206-0162-99
Zymfentra	infliximab-dyyb	J1748	72606-0025-01, 72606-0025-02, 72606-0025-10

Neupogen	filgrastim	J1442	54569-4824-00, 55513-0347-10, 55513-0348-01, 55513-0348-10, 55513-0347-01, 55513-0530-01, 55513-0530-10, 55513-0924-10, 55513-0924-91, 55513-0924-01, 55513-0209-91, 55513-0209-01, 55513-0209-10, 55513-0546-01, 55513-0546-10, 54868-2522-00, 54868-2522-01, 54868-5020-00, 54868-3050-00
Nivestym	filgrastim-aafi	Q5110	00069-0292-01, 00069-0292-10, 00069-0294-10, 00069-0293-01, 00069-0293-10, 00069-0294-01, 00069-0291-01, 00069-0291-10
Releuko	filgrastim-ayow	Q5125	70121-1569-01, 70121-1569-07, 70121-1568-01, 70121-1568-07, 70121-1570-01, 70121-1570-07, 70121-1571-01, 70121-1571-07
Zarxio	filgrastim-sndx	Q5101	61314-0304-01, 61314-0318-10, 61314-0304-10, 61314-0318-01, 61314-0326-05, 61314-0326-10, 61314-0312-10, 61314-0326-01, 61314-0312-01
Neulasta	pegfilgrastim	J2505 (until 2022q1)* J3506 (2022q1 and later)	55513-0190-01, 54868-5229-00
Fulphila	pegfilgrastim-jmdb	Q5108	67457-0833-06, 83257-0005-41
Fylnetra	pegfilgrastim-pbbk	Q5130	70121-1627-01
Nivepria	pegfilgrastim-apgf	Q5122	00069-0324-01
Stimufend	pegfilgrastim-fpgk	Q5127	65219-0371-10
Udenyca	pegfilgrastim-cbqv	Q5111	70114-0120-01, 70114-0101-01
Ziextenzo	pegfilgrastim-bmez	Q5120	61314-0866-01
Lucentis	ranibizumab	J2778	50242-0082-01, 50242-0082-02, 50242-0082-03, 50242-0080-03, 50242-0080-01, 50242-0080-02
Byooviz	ranibizumab-nuna	Q5124	64406-0019-01, 64406-0019-07
Cimerli	ranibizumab-eqrn	Q5128	70114-0441-01, 61314-0625-94, 61314-0624-94, 70114-0440-01
Rituxan	rituximab	J9310 (until 2019q1)‡ J9312 (2019q1 and later)	50242-0053-06, 50242-0051-10, 50242-0051-21
Riabni	rituximab-arrx	Q5119	55513-0326-01, 55513-0224-01
Ruxience	rituximab-pvvr	Q5115	00069-0249-01, 00069-0238-01
Truxima	rituximab-abbs	J9311	63459-0104-50, 63459-0103-10
Herceptin	trastuzumab	J9355	50242-0132-10, 50242-0132-01, 50242-0333-01, 50242-0134-60, 50242-0134-68
Herzuma	trastuzumab-pkrb	Q5113	63459-0305-47, 63459-0307-41, 63459-0303-43
Kanjinti	trastuzumab-anns	Q5117	55513-0132-01, 55513-0141-01, 55513-0164-01 (Kanjinti Kit)

Ogivri	trastuzumab-dkst	Q5114	67457-0847-44, 83257-0004-12, 67457-0991-15, 83257-0001-11, 67457-0845-50
Ontruzant	trastuzumab-dttb	Q5112	00006-5033-02, 00006-5034-02, 78206-0147-01, 78206-0148-01
Trazimera	trastuzumab-qyyp	Q5116	00069-0305-01, 00069-0308-01

"infliximab biosimilar" HCPCS code Q5102 excluded due to lack of an available brand name

* ASP values for Neulasta 6mg (HCPCS J2505, prior to 2023q1) were standardized to 0.5 mg for continuity and comparison of ASPs over time.

‡ ASP values for Rituxan 100 mg (HCPCS J9310) were standardized to 10 mg for continuity and comparison of ASPs over time

A2. Biosimilar Entry & Market Share: Incremental Changes

We used a linear regression using Equation A 1 to assess the relationship between the presence of each subsequent biosimilar entrant and the reference product market share. Each indicator ($\boldsymbol{bio1_t}$, $\boldsymbol{bio2_t}$, $\boldsymbol{bio3_t}$, etc.) is set to 1 in all quarters (**t**) where the biosimilar entrant is present (first, second, third, etc., respectively). The interpretation of each associated coefficient is the incremental change in reference product market share associated with the respective biosimilar entry (first, second, third, etc.). Biologic drug groups (also referred to as markets) were defined by molecule. For example, the rituximab drug group includes the reference product Rituxan® and the three rituximab biosimilars. Because of the large variance of group size across markets, we controlled for $\boldsymbol{log(TotalClaims)_{gt}}$ for each biologic group (**g**) in each quarter (**t**). We used this model for each drug group individually, as well as in the overall data with fixed effects for drug group.

Equation A 1. $$\boldsymbol{Ref\ product\ Mktshare = \beta_0 + \beta_1 bio1_t + \beta_2 bio2_t + \beta_3 bio3_t + \beta_4 bio4_t + \beta_5 bio5_t + \beta_6 bio6_t + \beta_7 log(TotalClaims)_{gt} + \varepsilon}$$

Table A 2. Incremental Change in Reference Product Market Share, Each Biosimilar Entry

	Medicare			Commercial		
Group	**Estimate**	**SE**	**Group**	**Estimate**	**SE**	**Group**
First Biosimilar						
Overall	-0.137	0.05437	0.039	-0.051	0.05797	0.408
Filgrastim	-0.342	0.06818	<0.001	**-0.196**	**0.06103**	**0.003**
Pegfilgrastim	**-0.054**	**0.01566**	**0.001**	-0.006	0.01007	0.579
Epoetin Alfa	-0.152	0.09215	0.108	**-0.074**	**0.0357**	**0.046**
Trastuzumab	**-0.131**	**0.0277**	**<0.001**	-0.0002	0.04294	0.996
Infliximab	**-0.149**	**0.00993**	**<0.001**	0.001	0.00192	0.761
Rituximab	-0.034	0.02194	0.135	**-0.147**	**0.06301**	**0.025**
Bevacizumab	-0.011	0.01064	0.3	**-0.159**	**0.04858**	**0.002**
Ranibizumab	**-0.066**	**0.01416**	**<0.001**	**-0.011**	**0.00365**	**0.006**
Second Biosimilar						
Overall	-0.123	0.07526	0.145	**-0.289**	**0.08185**	**0.01**
Filgrastim	**-0.165**	**0.07229**	**0.028**	-0.096	0.07907	0.235
Pegfilgrastim	**-0.166**	**0.0218**	**<0.001**	**-0.221**	**0.04597**	**<0.001**
Trastuzumab	**-0.167**	**0.02879**	**<0.001**	-0.02	0.04036	0.617
Infliximab	*N/A**	*N/A*	*N/A*	**-0.069**	**0.01296**	**<0.001**
Rituximab	**-0.305**	**0.05003**	**<0.001**	**-0.236**	**0.05924**	**<0.001**
Bevacizumab	**-0.095**	**0.01568**	**<0.001**	**-0.532**	**0.06932**	**<0.001**
Ranibizumab	*N/A*	*N/A*	*N/A*	**-0.167**	**0.07017**	**0.023**
Third Biosimilar						
Overall	-0.096	0.06834	0.202	**-0.178**	**0.06484**	**0.029**
Filgrastim	0.226	0.12804	0.086	**-0.058**	**0.01902**	**0.004**
Pegfilgrastim	**-0.072**	**0.01793**	**<0.001**	-0.014	0.03923	0.728
Trastuzumab	**-0.137**	**0.03845**	**0.001**	**-0.118**	**0.00589**	**<0.001**
Infliximab	**-0.116**	**0.013943**	**<0.001**	**-0.313**	**0.0484**	**<0.001**
Rituximab	**-0.177**	**0.04343**	**<0.001**	**-0.376**	**0.05472**	**<0.001**
Bevacizumab	0.021	0.02164	0.342	**-0.216**	**0.05629**	**<0.001**
Fourth Biosimilar						
Overall	-0.061	0.06346	0.369	**0.130**	**0.03568**	**0.008**
Pegfilgrastim	**-0.079**	**0.01507**	**<0.001**	**-0.035**	**0.00833**	**<0.001**
Trastuzumab	**-0.138**	**0.03939**	**0.001**	**-0.075**	**0.01146**	**<0.001**
Bevacizumab	0.001	0.01889	0.976	-0.009	0.00767	0.249
Fifth Biosimilar						
Overall	**-0.159**	**0.03459**	**0.002**	**-0.248**	**0.06711**	**0.008**
Pegfilgrastim	-0.013	0.00986	0.182	-0.003	0.00929	0.769
Trastuzumab	-0.04	0.01889	0.394	**-0.355**	**0.04003**	**<0.001**
Sixth Biosimilar						
Overall	*N/A*	*N/A*	*N/A*	0.061	0.09678	0.549
Pegfilgrastim	*N/A**	*N/A*	*N/A*	**-0.039**	**0.00154**	**<0.001**
Trastuzumab	*N/A*	*N/A*	*N/A*	**-0.087**	**0.03161**	**<0.001**

Figure A 1. Incremental Change in Reference Product Market Share, Medicare

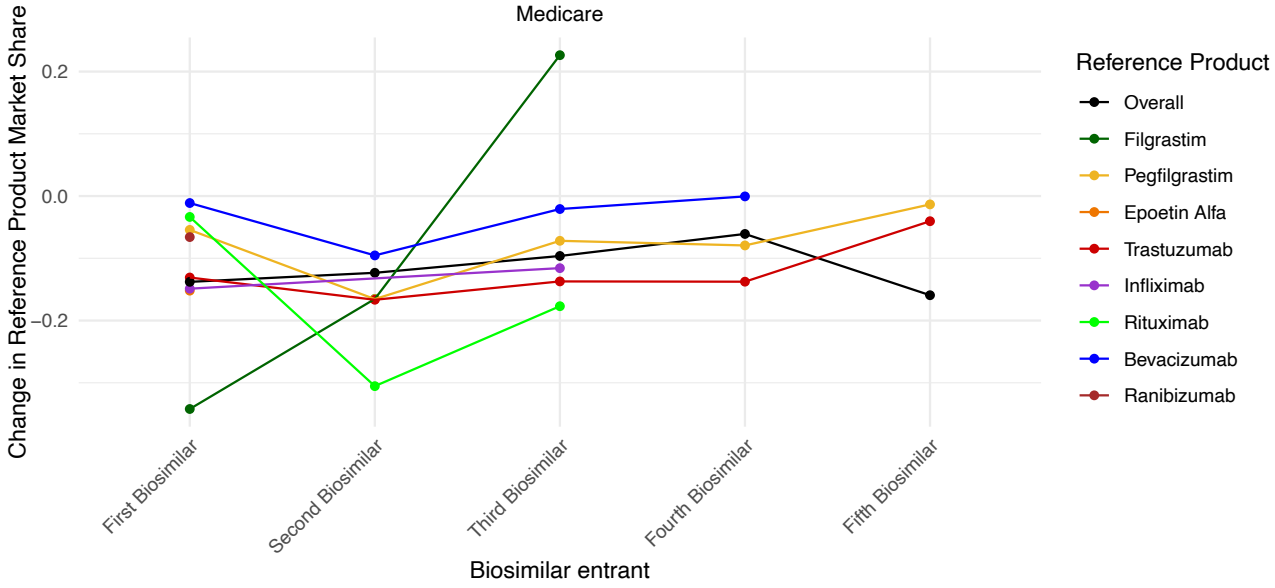
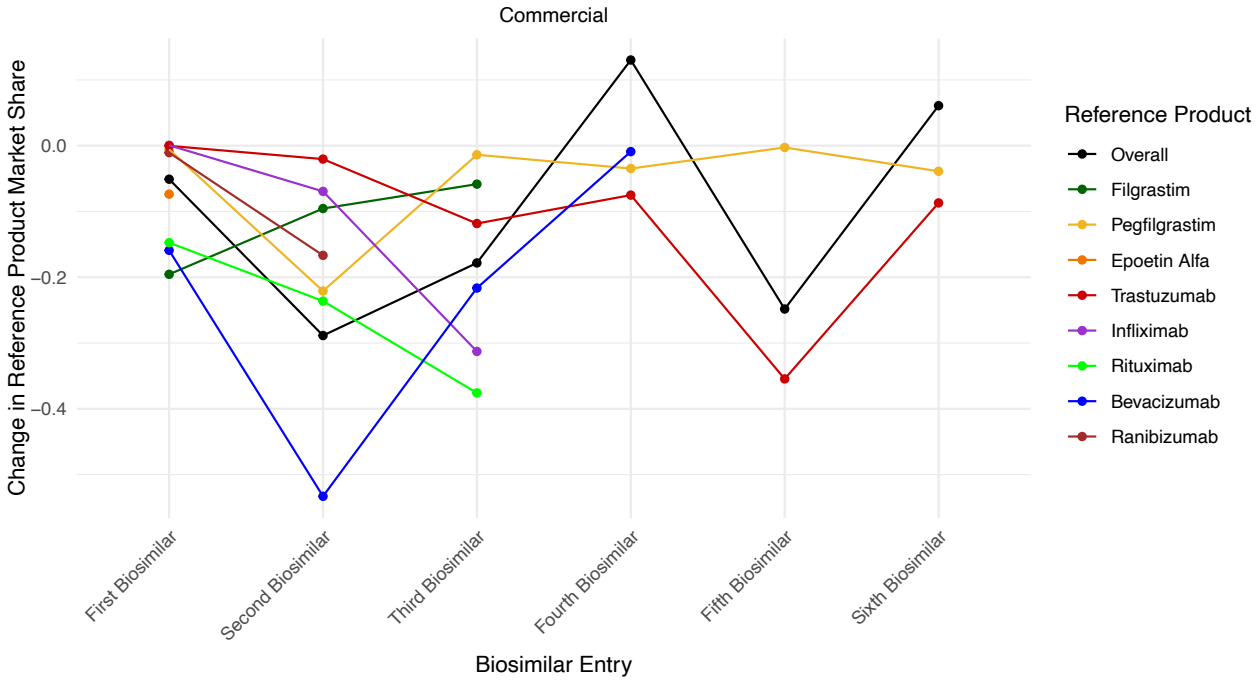


Figure A 2. Incremental Change in Reference Product Market Share, Commercial



A3. Leave-One-Out Analysis

For the price decline analysis, we conducted a leave-one-out analysis to identify whether a particular market was driving the results in the overall analysis.

In Medicare, leaving out filgrastim led to the largest difference from the full model, but still indicated that biosimilars' prices declined faster than reference products and the scaled difference in standard error units indicated that it was within an acceptable range (see Table A 3, Figure A 3, and Figure A 4).

Table A 3. LOO Price Decline – Medicare

Model	**Bio coefficient**
Original (all included)	-0.186 (p<0.001)
Without Filgrastim	-0.128 (p=0.006)
Without Pegfilgrastim	-0.222 (p<0.001)
Without Infliximab	-0.220 (p<0.001)
Without Rituximab	-0.174 (p=0.003)
Without Trastuzumab	-0.171 (p=0.003)
Without Epoetin Alfa	-0.206 (p<0.001)
Without Bevacizumab	-0.176 (p=0.002)
Without Ranibizumab	-0.189 (p<0.001)

Figure A 3. LOO Analysis, % Difference from Full Model - Medicare

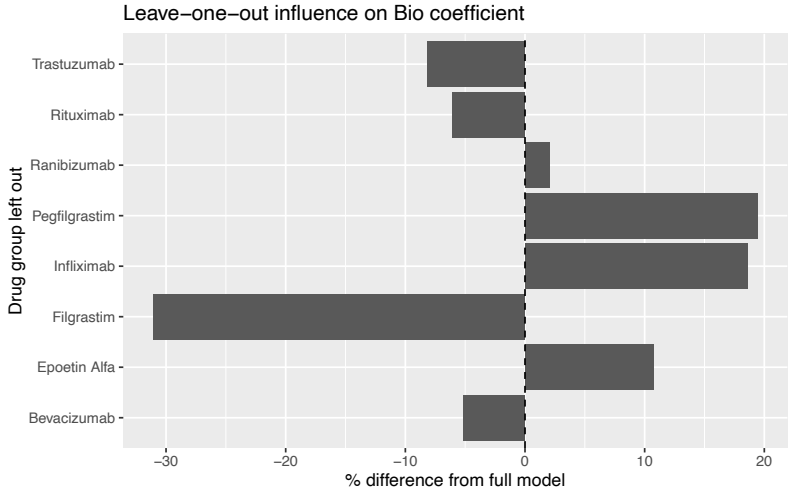
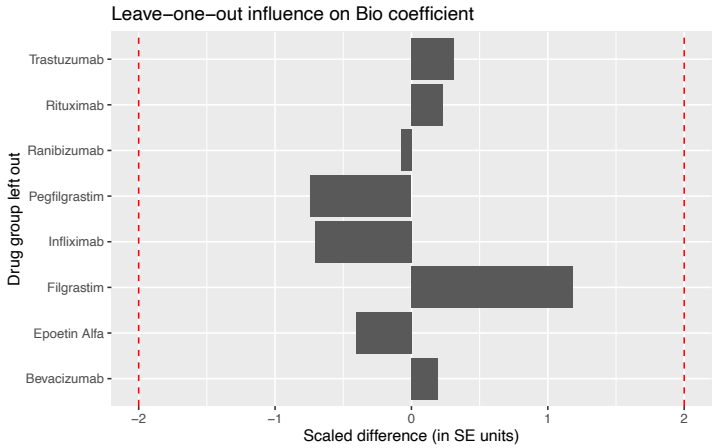


Figure A 4. LOO Analysis, Scaled Difference (SE units) – Medicare



The overall estimate for the commercial sector was not statistically significant. We still conducted the leave-one-out analysis, to identify whether one market might be skewing the results. In commercial, multiple of the markets seemed to have an influence, but due to the wide confidence interval for the original estimate the scaled difference for all were still within two SE units (see Table A 4, Figure A 5, and Figure A 6).

Table A 4. LOO Price Decline – Commercial

Model	**Bio coefficient**
Original (all included)	-0.063 (p=0.538)
Without Filgrastim	-0.088 (p=0.142)
Without Pegfilgrastim	-0.038 (p=0.752)
Without Infliximab	-0.102 (p=0.436)
Without Rituximab	-0.034 (p=0.762)
Without Trastuzumab	-0.020 (p=0.859)
Without Epoetin Alfa	-0.059 (p=0.607)
Without Bevacizumab	-0.035 (p=0.757)
Without Ranibizumab	-0.063 (p=0.550)

Figure A 5. LOO Analysis, % Difference from Full Model - Commercial

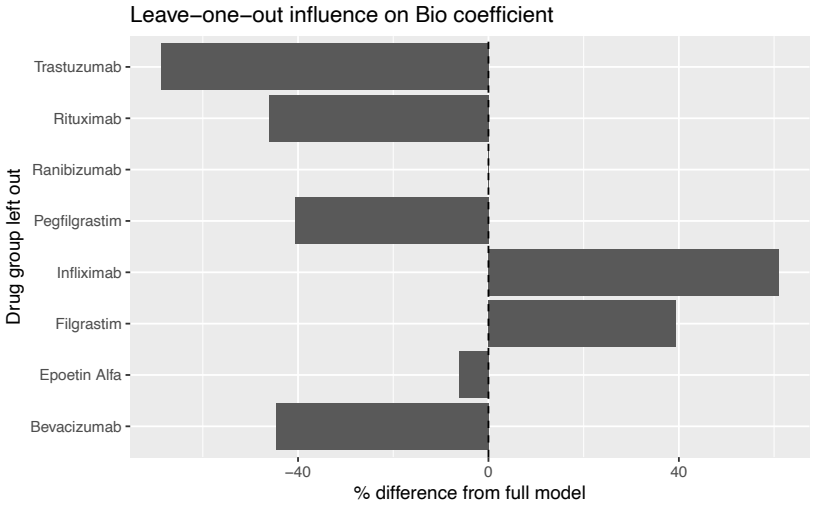
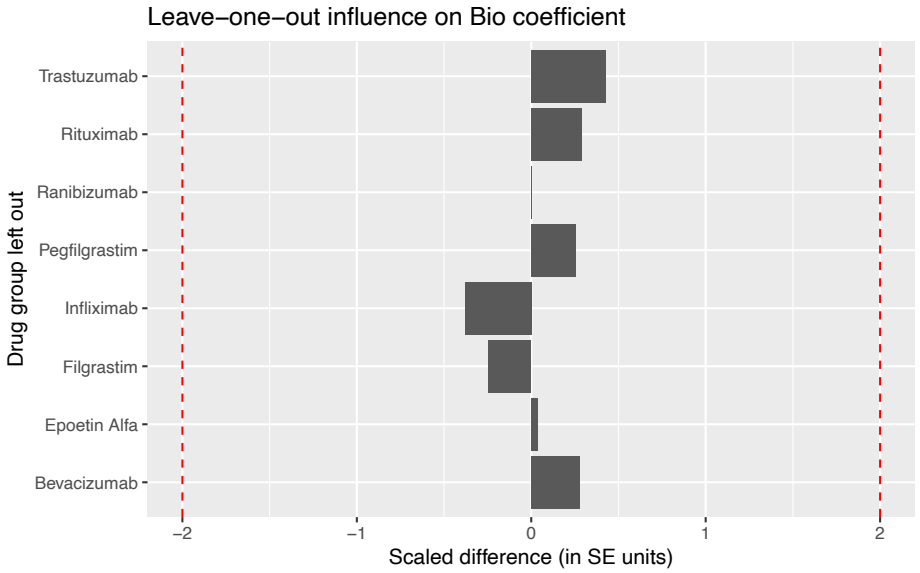


Figure A 6. LOO Analysis, Scaled Difference (SE units) – Commercial



Appendix B: Chapter 2 Appendix

B1. Identification of Controls

Clinical Guidelines Reviewed

- 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis[53]
- 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis[54]
- Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics[55]
- ACG Clinical Guideline Update: Ulcerative Colitis in Adults[56]
- ACG Clinical Guideline: Management of Crohn's Disease in Adults[57]

Indications of Included Biologics

Table B 1. Included Biologics

Nonproprietary name	Brand name	MOA	Admin		Indications						
			IV	SQ	RA	PsA	Ps	AS	CD	UC	Other
Adalimumab	Humira[58]	TNF blocker	N	Y	Y	Y	Y	Y	Y	Y	Y
Infliximab	Remicade[59]	TNF blocker	Y	N*	Y	Y	Y	Y	Y	Y	N
Rituximab	Rituxan[60]	Anti-CD20	Y	N	Y	N	N	N	N	N	Y
Abatacept	Orencia[61]	Selective T cell costimulation modulator	Y	Y	Y	Y	N	N	N	N	Y
Anakinra	Kineret[62]	IL-1 inhibitor	N	Y	Y	N	N	N	N	N	Y
Bimekizumab	Bimzelx[63]	IL-17A and IL-17F inhibitor	N	Y	N	Y	Y	Y	N	N	Y
Brodalumab	Siliq[64]	IL-17A inhibitor	N	Y	N	N	Y	N	N	N	N
Canakinumab	Ilaris[65]	IL-1beta inhibitor**	N	Y	N	N	N	N	N	N	Y
Certolizumab pegol	Cimzia[66]	TNF blocker	N	Y	Y	Y	Y	Y	Y	N	Y
Etanercept	Enbrel[67]	TNF blocker	N	Y	Y	Y	Y	Y	N	N	N
Golimumab	Simponi Aria[68]	TNF blocker	Y	N	Y	Y	N	Y	N	N	Y
Golimumab	Simponi[69]	TNF blocker	N	Y	Y	Y	N	Y	N	Y	N
Guselkumab	Tremfya[70]	IL-23 inhibitor	Y	Y	N	Y	Y	N	N	Y	N
Ixekizumab	Taltz[71]	IL-17A inhibitor	N	Y	N	Y	Y	Y	N	N	Y
Natalizumab	Tysabri[72]	Integrin receptor antagonist	Y	N	N	N	N	N	Y	N	Y
Rilonacept	Arcalyst[73]	IL-1 inhibitor**	N	Y	N	N	N	N	N	N	Y
Risankizumab	Skyrizi[74]	IL-23 inhibitor	Y	Y	N	Y	Y	N	Y	Y	N
Sarilumab	Kevzara[75]	IL-6 inhibitor	N	Y	Y	N	N	N	N	N	Y
Secukinumab	Cosentyx[76]	IL-17A inhibitor	Y	Y	N	Y	Y	Y	N	N	Y
Tocilizumab	Actemra[77]	IL-6 inhibitor	Y	Y	Y	N	N	N	N	N	Y
Ustekinumab	Stelara[78]	IL-12 and IL-23 inhibitor	N	Y	N	Y	Y	N	Y	Y	N
Vedolizumab	Entyvio[79]	Integrin receptor antagonist	Y	Y	N	N	N	N	Y	Y	N

* the infliximab biosimilar Zymfentra (infliximab-dyyb) is included in this analysis and is available as a subcutaneous injection but only has indications for Crohn's Disease and Ulcerative Colitis.
**Canakinumab and rilonacept were included based on mechanism of action and potential for off-label use. Very few patients in the control group were using these two, and leaving either or both out of the analysis did not meaningfully change results.
Key: IV – intravenous; SQ – subcutaneous; RA – Rheumatoid Arthritis; PsA – Psoriatic Arthritis; Ps – Plaque Psoriasis; AS – Ankylosing Spondylitis; CD – Crohn's Disease; UC – Ulcerative Colitis; Other – includes hidradenitis suppurativa, uveitis, juvenile idiopathic arthritis, oncology indications (rituximab), giant cell arteritis, systemic sclerosis-associated interstitial lung disease, cytokine release syndrome, COVID-19, multiple sclerosis, polymyalgia rheumatica, acute graft versus host disease, cryopyrin-associated periodic syndromes, deficiency of IL-1 receptor antagonist, and non-radiographic axial spondyloarthritis, enthesitis-related arthritis.

B2. Drug Identifiers

Table B 2. Drug Identifiers

Non-proprietary name	Brand Name	HCPCS	NDCs
adalimumab	Humira	J0135	00074-0067-02, 00074-0124-02, 00074-0124-03, 00074-0124-04, 00074-0243-02, 00074-0554-02, 00074-0616-02, 00074-0817-02, 00074-1539-03, 00074-2540-03, 00074-3799-01, 00074-3799-02, 00074-3799-03, 00074-3799-06, 00074-4339-02, 00074-4339-06, 00074-4339-07, 00074-6347-02, 00074-9374-02, 50090-4487-00, 54569-5524-00, 54868-4822-00, 83457-0123-01, 83457-0124-02, 83457-0242-01, 83457-0243-02, 83457-0553-01, 83457-0554-02, 83457-0615-01, 83457-0616-02, 83457-0816-01, 83457-0817-02
adalimumab-atto	Amjevita	N/A*	55513-0399-01, 55513-0400-01, 55513-0400-02, 55513-0410-01, 55513-0411-01, 55513-0413-01, 55513-0479-01, 55513-0479-02, 55513-0481-01, 55513-0481-02, 55513-0482-01, 55513-0482-02, 72511-0399-01, 72511-0400-01, 72511-0400-02, 72511-0479-01, 72511-0479-02, 72511-0481-01, 72511-0481-02, 72511-0482-01, 72511-0482-02, 84612-0399-01, 84612-0479-02, 84612-0481-02, 84612-0482-02
adalimumab-adbm	Cyltezo	Q5143	00597-0370-82, 00597-0375-16, 00597-0375-23, 00597-0375-97, 00597-0400-89, 00597-0405-80, 00597-0485-20, 00597-0495-40, 00597-0495-50, 00597-0495-60, 00597-0545-22, 00597-0545-44, 00597-0545-66, 00597-0555-80, 00597-0565-20, 00597-0575-40, 00597-0575-50, 00597-0575-60, 00597-0585-89, 00597-0595-20, 82009-0144-22, 82009-0146-22, 82009-0148-22, 82009-0150-22
adalimumab-adaz	Hyrimoz	N/A*	61314-0325-20, 61314-0325-96, 61314-0327-20, 61314-0327-64, 61314-0332-64, 61314-0332-94, 61314-0454-20, 61314-0454-36, 61314-0454-68, 61314-0473-20, 61314-0473-64, 61314-0476-64, 61314-0509-64, 61314-0517-36, 61314-0531-64, 83457-0100-01, 83457-0101-01, 83457-0102-01, 83457-0103-01, 83457-0107-01, 83457-0108-01, 83457-0112-01, 83457-0113-01, 83457-0200-40, 83457-0201-46, 83457-0202-50, 83457-0203-56
adalimumab-bwwd	Hadlima	N/A*	78206-0183-01, 78206-0184-01, 78206-0186-01, 78206-0187-01
adalimumab-afzb	Abrilada	Q5145	00025-0317-01, 00025-0318-01, 00025-0325-01, 00025-0325-02, 00025-0328-02, 00025-0329-01, 00025-0333-02, 00069-0325-01, 00069-0325-02, 00069-0328-02, 00069-0333-02
adalimumab-fkjp	Hulio	Q5140	49502-0380-02, 49502-0380-06, 49502-0381-02, 49502-0381-06, 49502-0382-02, 49502-0382-06, 49502-0416-02, 49502-0417-02, 49502-0418-02, 83257-0016-42, 83257-0017-42, 83257-0019-32, 83257-0020-42, 83257-0021-42, 83257-0022-32
adalimumab-aqvh	Yusimry	N/A*	70114-0220-02
adalimumab-aacf	Idacio	Q5131	65219-0554-08, 65219-0554-28, 65219-0554-38, 65219-0556-18, 65219-0574-04, 65219-0610-02, 65219-0612-69, 65219-0612-89, 65219-0612-99, 65219-0618-02, 65219-0620-20
adalimumab-aaty	Yuflyma	Q5141	72606-0022-06, 72606-0022-09, 72606-0022-10, 72606-0023-04, 72606-0023-07, 72606-0024-01, 72606-0030-06, 72606-0030-09, 72606-0030-10, 72606-0040-04, 72606-0041-01
adalimumab-ryvk	Simlandi	Q5142	51759-0386-22, 51759-0402-02, 51759-0402-17, 51759-0412-22, 51759-0497-31, 51759-0523-21, 51759-0624-31, 51759-0634-31, 82009-0156-22, 82009-0158-22
infliximab	Remicade	J1745	57894-0160-01, 57894-0030-01
infliximab-aqqx	Avsola	Q5121	55513-0670-01
infliximab-dyyb	Inflectra	Q5103	00069-0809-01
infliximab-abda	Renflexis	Q5104	00006-4305-02, 78206-0162-01, 78206-0162-99

infliximab-dyyb	Zymfentra	J1748	72606-0025-01, 72606-0025-02, 72606-0025-10
rituximab	Rituxan	J9310 (until 2019q1) J9312 (after 2019q1)	50242-0053-06, 50242-0051-10, 50242-0051-21
rituximab-arrx	Riabni	Q5119	55513-0326-01, 55513-0224-01
rituximab-pvvr	Ruxience	Q5115	00069-0249-01, 00069-0238-01
rituximab-abbs	Truxima	J9311	63459-0104-50, 63459-0103-10
Abatacept	Orencia	J0129	00003-2187-10, 00003-2187-13, 00003-2188-11, 00003-2188-31, 00003-2188-51, 00003-2814-11, 00003-2818-11
Anakinra	Kineret	N/A*	55513-0177-01, 55513-0177-07, 55513-0177-28, 66658-0234-01, 66658-0234-07, 66658-0234-28
Bimekizumab	Bimzelx	N/A*	50474-0782-84, 50474-0782-86, 50474-0781-84, 50474-0781-85, 50474-0783-78, 50474-0780-79, 50474-0780-78
Brodalumab	Siliq	N/A*	00187-0004-00, 00187-0004-02
Canakinumab	Ilaris	J0638	00078-0582-61, 00078-0734-61
Certolizumab	Cimzia	J0717	50474-0700-62, 50474-0710-79, 50474-0710-81
Etanercept	Enbrel	J1438	50090-4490-00, 50090-4590-00, 58406-0055-04, 58406-0055-01, 58406-0425-34, 58406-0425-41, 58406-0455-01, 58406-0435-04, 58406-0445-01, 58406-0445-04, 58406-0021-01, 58406-0435-01, 58406-0032-01, 58406-0032-04, 58406-0010-01, 58406-0010-04, 58406-0455-04, 58406-0021-04, 54868-4782-00, 54868-5444-00, 58406-0456-04, 58406-0044-01, 58406-0044-04, 58406-0456-01
Golimumab	Simponi, Simponi Aria	J1602	57894-0070-01, 57894-0070-02, 57894-0071-01, 57894-0071-02, 57894-0350-01
Guselkumab	Tremfya	J1628	57894-0640-01, 57894-0640-11, 57894-0650-01, 57894-0650-02, 57894-0651-01, 57894-0651-02, 57894-0651-11, 57894-0651-22
Ixekizumab	Taltz	N/A*	00002-1445-01, 00002-1445-09, 00002-1445-11, 00002-1445-27, 00002-1445-61, 00002-7724-01, 00002-7724-09, 00002-7724-11, 00002-7724-27, 00002-8900-01, 00002-8900-11, 00002-8905-01, 00002-8905-11
Natalizumab	Tysabri	J2323	59075-0730-15, 64406-0008-01
Rilonacept	Arcalyst	J2793	61755-0001-01, 73604-0914-01, 73604-0914-04
Risankizumab		J2327	00074-2042-01, 00074-2042-02, 00074-1050-01, 00074-2100-01, 00074-1065-01, 00074-1066-01, 00074-1070-01, 00074-1069-01, 00074-5015-01
Sarilumab	Kevzara	N/A*	00024-5910-01, 00024-5922-01, 00024-5908-01, 00024-5920-01
Secukinumab	Cosentyx	N/A*	00078-0639-68, 00078-0639-41, 00078-0639-98, 00078-0639-97, 00078-1056-97, 00078-1168-61, 00078-1070-68
Tocilizumab	Actemra	J3262	50242-0138-01, 50242-0137-01, 50242-0135-01, 50242-0136-01, 50242-0143-01
Ustekinumab	Stelara	J3357, J3358	57894-0054-27, 57894-0060-02, 57894-0060-03, 57894-0061-03
Vedolizumab	Entyvio	J3380	64764-0108-21, 64764-0300-20

B3. Cohort

Table B 3. Patient Inclusion and Exclusion

Criteria	Intervention	Control
2 qualifying drug claims for the same drug in each year of inclusion	897,576 PYs 405,906 patients	807,377 PYs 329,080 patients
Exclude patients who appear in two drug groups in the same year	823,390 PYs 381,102 patients	693,750 PYs 305,113 patients
Enrolled for full year, each year of inclusion	680,675 PYs 315,910 patients	574,660 PYs 252,240 patients
Exclude patients who appear in two drug groups ever	572,404 PYs 270,471 patients	413,873 PYs 196,224 patients
Sum claims within each table by service date, remove negatives	572,206 PYs 270,352 patients	413,464 PYs 196,007 patients

Key: PYs – patient-years

Table B 4. Patient Counts, by Drug Group

	Drug Group	Patient-Years	Patients
Intervention	Adalimumab	317,429	144,106
	Infliximab	175,435	73,729
	Rituximab	79,344	52,518
Control	Abatacept	27,419	13,146
	Anakinra	1,703	867
	Bimekizumab	0	0
	Brodalumab	85	62
	Canakinumab	1,000	427
	Certolizumab	17,849	9,323
	Etanercept	177,971	75,900
	Golimumab	20,302	10,050
	Guselkumab	11,632	6,816
	Ixekizumab	10,748	6,311
	Natalizumab	36,452	16,108
	Rilonacept	203	135
	Risankizumab	14,990	9,917
	Sarilumab	853	548
	Secukinumab	14,041	8,079
	Tocilizumab	11,601	6,006
	Ustekinumab	45,033	21,404
	Vedolizumab	21,582	10,908

Table B 5. Patient Characteristics, by Year

	2011		2012		2013		2014	
	Control (N=38508)	Intervention (N=53022)	Control (N=40507)	Intervention (N=57218)	Control (N=33698)	Intervention (N=47659)	Control (N=35271)	Intervention (N=54755)
mAGE								
Mean (SD)	47.5 (11.8)	45.7 (13.3)	47.2 (11.9)	45.2 (13.5)	47.5 (12.0)	45.0 (13.7)	47.5 (12.1)	44.7 (13.9)
Median [Min, Max]	50.0 [1.00, 64.0]	49.0 [0, 64.0]	50.0 [0, 64.0]	48.0 [0, 64.0]	50.0 [0, 64.0]	48.0 [0, 64.0]	50.0 [1.00, 64.0]	48.0 [0, 64.0]
factor(SEX)								
1	14173 (36.8%)	23409 (44.1%)	14818 (36.6%)	25783 (45.1%)	12440 (36.9%)	21513 (45.1%)	12927 (36.7%)	24950 (45.6%)
2	24335 (63.2%)	29613 (55.9%)	25689 (63.4%)	31435 (54.9%)	21258 (63.1%)	26146 (54.9%)	22344 (63.3%)	29805 (54.4%)
factor(plan)								
EPO	813 (2.1%)	1235 (2.3%)	539 (1.3%)	923 (1.6%)	492 (1.5%)	874 (1.8%)	450 (1.3%)	880 (1.6%)
HDHP	801 (2.1%)	1134 (2.1%)	1071 (2.6%)	1561 (2.7%)	1445 (4.3%)	2098 (4.4%)	1738 (4.9%)	2683 (4.9%)
HMO	4857 (12.6%)	5933 (11.2%)	4477 (11.1%)	5743 (10.0%)	4767 (14.1%)	6337 (13.3%)	3153 (8.9%)	4900 (8.9%)
Multiple	326 (0.8%)	424 (0.8%)	332 (0.8%)	431 (0.8%)	276 (0.8%)	402 (0.8%)	370 (1.0%)	603 (1.1%)
Other	7924 (20.6%)	10829 (20.4%)	8117 (20.0%)	11321 (19.8%)	6198 (18.4%)	8419 (17.7%)	8532 (24.2%)	13192 (24.1%)
PPO	23787 (61.8%)	33467 (63.1%)	25971 (64.1%)	37239 (65.1%)	20520 (60.9%)	29529 (62.0%)	21028 (59.6%)	32497 (59.3%)

2015		2016		2017		2018		2019	
Control (N=24429)	Intervention (N=38761)	Control (N=25651)	Intervention (N=41604)	Control (N=25559)	Intervention (N=42310)	Control (N=28263)	Intervention (N=44312)	Control (N=30194)	Intervention (N=43827)
47.8 (12.2)	44.7 (14.0)	47.7 (12.4)	44.4 (14.2)	47.3 (12.6)	44.1 (14.3)	46.9 (12.6)	43.6 (14.4)	46.5 (12.6)	43.4 (14.5)
51.0 [0, 64.0]	48.0 [0, 64.0]	50.0 [1.00, 64.0]	47.0 [0, 64.0]	50.0 [1.00, 64.0]	47.0 [0, 64.0]	49.0 [1.00, 64.0]	46.0 [1.00, 64.0]	49.0 [0, 64.0]	46.0 [1.00, 64.0]
8829 (36.1%)	17878 (46.1%)	9508 (37.1%)	19434 (46.7%)	9594 (37.5%)	20019 (47.3%)	10964 (38.8%)	21114 (47.6%)	11955 (39.6%)	20798 (47.5%)
15600 (63.9%)	20883 (53.9%)	16143 (62.9%)	22170 (53.3%)	15965 (62.5%)	22291 (52.7%)	17299 (61.2%)	23198 (52.4%)	18239 (60.4%)	23029 (52.5%)
223 (0.9%)	347 (0.9%)	213 (0.8%)	330 (0.8%)	245 (1.0%)	387 (0.9%)	245 (0.9%)	360 (0.8%)	275 (0.9%)	363 (0.8%)
1286 (5.3%)	2033 (5.2%)	1897 (7.4%)	3118 (7.5%)	2261 (8.8%)	3776 (8.9%)	2733 (9.7%)	4648 (10.5%)	3352 (11.1%)	5134 (11.7%)
2220 (9.1%)	3533 (9.1%)	2286 (8.9%)	3593 (8.6%)	2303 (9.0%)	4040 (9.5%)	3032 (10.7%)	5018 (11.3%)	3284 (10.9%)	5054 (11.5%)
260 (1.1%)	377 (1.0%)	256 (1.0%)	403 (1.0%)	165 (0.6%)	264 (0.6%)	173 (0.6%)	187 (0.4%)	181 (0.6%)	218 (0.5%)
5637 (23.1%)	8833 (22.8%)	5653 (22.0%)	9218 (22.2%)	6094 (23.8%)	10360 (24.5%)	7578 (26.8%)	11809 (26.6%)	7209 (23.9%)	10126 (23.1%)
14803 (60.6%)	23638 (61.0%)	15346 (59.8%)	24942 (60.0%)	14491 (56.7%)	23483 (55.5%)	14502 (51.3%)	22290 (50.3%)	15893 (52.6%)	22932 (52.3%)

2020		2021		2022		2023		Overall	
Control (N=26094)	Intervention (N=35059)	Control (N=30724)	Intervention (N=37171)	Control (N=34331)	Intervention (N=37433)	Control (N=40235)	Intervention (N=39075)	Control (N=413464)	Intervention (N=572206)
46.1 (12.7)	43.0 (14.7)	45.9 (12.7)	42.9 (14.7)	45.9 (12.6)	42.7 (14.8)	45.6 (12.6)	42.4 (14.8)	46.9 (12.4)	44.1 (14.2)
48.0 [0, 64.0]	46.0 [0, 64.0]	48.0 [1.00, 64.0]	45.0 [0, 64.0]	48.0 [0, 64.0]	45.0 [0, 64.0]	48.0 [0, 64.0]	45.0 [0, 64.0]	49.0 [0, 64.0]	47.0 [0, 64.0]
10569 (40.5%)	16359 (46.7%)	12674 (41.3%)	17210 (46.3%)	14398 (41.9%)	17124 (45.7%)	16953 (42.1%)	17710 (45.3%)	159802 (38.6%)	263301 (46.0%)
15525 (59.5%)	18700 (53.3%)	18050 (58.7%)	19961 (53.7%)	19933 (58.1%)	20309 (54.3%)	23282 (57.9%)	21365 (54.7%)	253662 (61.4%)	308905 (54.0%)
192 (0.7%)	255 (0.7%)	292 (1.0%)	369 (1.0%)	302 (0.9%)	300 (0.8%)	257 (0.6%)	251 (0.6%)	4538 (1.1%)	6874 (1.2%)
2793 (10.7%)	3883 (11.1%)	3465 (11.3%)	4314 (11.6%)	4299 (12.5%)	4653 (12.4%)	4716 (11.7%)	4609 (11.8%)	31857 (7.7%)	43644 (7.6%)
3406 (13.1%)	4801 (13.7%)	3883 (12.6%)	5051 (13.6%)	4098 (11.9%)	5023 (13.4%)	5004 (12.4%)	5746 (14.7%)	46770 (11.3%)	64772 (11.3%)
708 (2.7%)	946 (2.7%)	162 (0.5%)	176 (0.5%)	192 (0.6%)	176 (0.5%)	196 (0.5%)	150 (0.4%)	3597 (0.9%)	4757 (0.8%)
6605 (25.3%)	8487 (24.2%)	7636 (24.9%)	8663 (23.3%)	8681 (25.3%)	8680 (23.2%)	10156 (25.2%)	8921 (22.8%)	96020 (23.2%)	128858 (22.5%)
12390 (47.5%)	16687 (47.6%)	15286 (49.8%)	18598 (50.0%)	16759 (48.8%)	18601 (49.7%)	19906 (49.5%)	19398 (49.6%)	230682 (55.8%)	323301 (56.5%)

B4. Biologic OOP Average Treatment Effect, Detailed Results

Table B 6. Group-Time Average Treatment Effect, Biologic OOP (raw results)

Group	Time	ATT(g,t)	Std. Error	L 95%	U 95%	Sig
2016	2012	28.92	18.28	-29.26	87.10	
2016	2013	88.26	18.91	28.06	148.46	*
2016	2014	-38.63	22.76	-111.08	33.82	
2016	2015	74.69	27.50	-12.83	162.22	
2016	**2016**	**-126.99**	**31.10**	**-226.00**	**-27.99**	*
2016	**2017**	**-199.49**	**34.86**	**-310.46**	**-88.51**	*
2016	**2018**	**-332.26**	**36.61**	**-448.80**	**-215.71**	*
2016	**2019**	**-385.48**	**40.93**	**-515.75**	**-255.20**	*
2016	**2020**	**-922.89**	**51.20**	**-1085.86**	**-759.93**	*
2016	**2021**	**-1834.69**	**49.70**	**-1992.90**	**-1676.49**	*
2016	**2022**	**-2876.36**	**50.61**	**-3037.48**	**-2715.25**	*
2016	**2023**	**-2393.03**	**48.17**	**-2546.35**	**-2239.71**	*
2019	2012	-28.36	30.21	-124.52	67.81	
2019	2013	-42.35	32.34	-145.30	60.60	
2019	2014	-96.38	32.05	-198.40	5.64	
2019	2015	-89.38	39.10	-213.83	35.07	
2019	2016	-222.49	42.01	-356.23	-88.76	*
2019	2017	-264.86	39.12	-389.39	-140.33	*
2019	2018	-82.19	48.27	-235.83	71.46	
2019	**2019**	**-296.97**	**41.40**	**-428.75**	**-165.19**	*
2019	**2020**	**-731.16**	**49.80**	**-889.68**	**-572.63**	*
2019	**2021**	**-1637.63**	**63.31**	**-1839.14**	**-1436.12**	*
2019	**2022**	**-2516.83**	**67.04**	**-2730.24**	**-2303.43**	*
2019	**2023**	**-2005.57**	**58.82**	**-2192.81**	**-1818.34**	*
2023	2012	-33.21	13.74	-76.93	10.52	
2023	2013	-23.72	17.03	-77.93	30.49	
2023	2014	5.69	17.95	-51.46	62.83	
2023	2015	-11.47	19.79	-74.47	51.53	
2023	2016	70.03	36.40	-45.85	185.90	
2023	2017	-32.64	37.13	-150.82	85.54	
2023	2018	372.54	30.70	274.81	470.28	*
2023	2019	25.85	37.09	-92.21	143.92	
2023	2020	73.34	48.96	-82.51	229.19	
2023	2021	10.99	55.69	-166.29	188.28	
2023	2022	539.32	63.60	336.86	741.77	*
2023	**2023**	**-375.01**	**65.83**	**-584.56**	**-165.47**	*

Key: Significance noted by * indicates 95% CI does not cross zero; Group 2018 = infliximab; Group 2019 = rituximab; Group 2023 = adalimumab; Bolded values indicate post-period

Table B 7. Average Effect by Length of Exposure, Biologic OOP (event study)

Event time	Estimate	Std. Err.	L 95%	U 95%	Sig
-11	-33.21	14.95	-76.53	10.11	
-10	-23.72	17.52	-74.48	27.03	
-9	5.69	18.06	-46.64	58.02	
-8	-11.47	21.46	-73.66	50.71	
-7	43.75	28.14	-37.79	125.29	
-6	-35.23	28.55	-117.97	47.50	
-5	247.30	26.30	171.09	323.50	*
-4	4.31	21.25	-57.28	65.89	
-3	19.94	26.77	-57.64	97.52	
-2	-56.12	33.21	-152.36	40.11	
-1	291.88	40.52	174.46	409.29	*
0	**-292.21**	**38.56**	**-403.95**	**-180.48**	*
1	**-420.66**	**28.59**	**-503.50**	**-337.81**	*
2	**-875.28**	**28.78**	**-958.68**	**-791.87**	*
3	**-1272.10**	**33.98**	**-1370.55**	**-1173.64**	*
4	**-1373.28**	**35.92**	**-1477.37**	**-1269.19**	*
5	**-1834.69**	**53.61**	**-1990.03**	**-1679.35**	*
6	**-2876.36**	**54.65**	**-3034.72**	**-2718.00**	*
7	**-2393.03**	**48.92**	**-2534.79**	**-2251.27**	*

Key: Significance noted by * indicates 95% CI does not cross zero; Bolded values indicate post-period

B5. Annual Total OOP Detailed Results

Table B 8. Group-Time Average Treatment Effect, Annual Total OOP (raw results)

Group	Time	ATT(g,t)	Std. Error	L 95%	U 95%	Sig
2016	2012	75.17	31.70	-21.64	171.97	
2016	2013	40.67	39.43	-79.76	161.09	
2016	2014	-77.50	33.08	-178.53	23.53	
2016	2015	202.01	38.54	84.30	319.72	*
2016	2016	-168.50	40.90	-293.42	-43.58	*
2016	2017	-282.58	44.65	-418.94	-146.21	*
2016	2018	-420.28	49.29	-570.82	-269.75	*
2016	2019	-477.39	52.56	-637.89	-316.89	*
2016	2020	-898.14	59.60	-1080.15	-716.14	*
2016	2021	-1876.58	58.59	-2055.49	-1697.66	*
2016	2022	-2900.76	58.91	-3080.66	-2720.86	*
2016	2023	-2380.75	55.86	-2551.34	-2210.17	*
2019	2012	-61.01	57.59	-236.87	114.86	
2019	2013	-67.03	67.31	-272.60	138.54	
2019	2014	-165.92	67.11	-370.86	39.03	
2019	2015	170.14	62.62	-21.09	361.37	
2019	2016	-176.81	63.35	-370.28	16.67	
2019	2017	-271.34	74.30	-498.26	-44.42	*
2019	2018	-187.45	77.27	-423.43	48.52	
2019	**2019**	**-200.82**	**62.80**	**-392.62**	**-9.02**	*
2019	**2020**	**-686.69**	**78.72**	**-927.10**	**-446.28**	*
2019	**2021**	**-1513.82**	**84.58**	**-1772.13**	**-1255.50**	*
2019	**2022**	**-2442.03**	**90.05**	**-2717.04**	**-2167.01**	*
2019	**2023**	**-1976.90**	**86.64**	**-2241.50**	**-1712.31**	*
2023	2012	-12.82	24.57	-87.86	62.22	
2023	2013	-43.81	27.76	-128.60	40.97	
2023	2014	60.03	27.37	-23.56	143.61	
2023	2015	-40.82	29.40	-130.62	48.97	
2023	2016	14.97	38.06	-101.27	131.21	
2023	2017	-41.80	38.40	-159.08	75.49	
2023	2018	333.63	38.42	216.29	450.97	*
2023	2019	48.83	39.33	-71.27	168.93	
2023	2020	93.64	50.37	-60.18	247.45	
2023	2021	-2.70	56.89	-176.43	171.03	
2023	2022	546.19	67.73	339.34	753.03	*
2023	**2023**	**-398.48**	**71.63**	**-617.22**	**-179.74**	*

Key: Significance noted by * indicates 95% CI does not cross zero; Group 2018 = infliximab; Group 2019 = rituximab; Group 2023 = adalimumab; Bolded values indicate post-period

Figure B 1. Group-Time Average Treatment Effect, Total Annual OOP

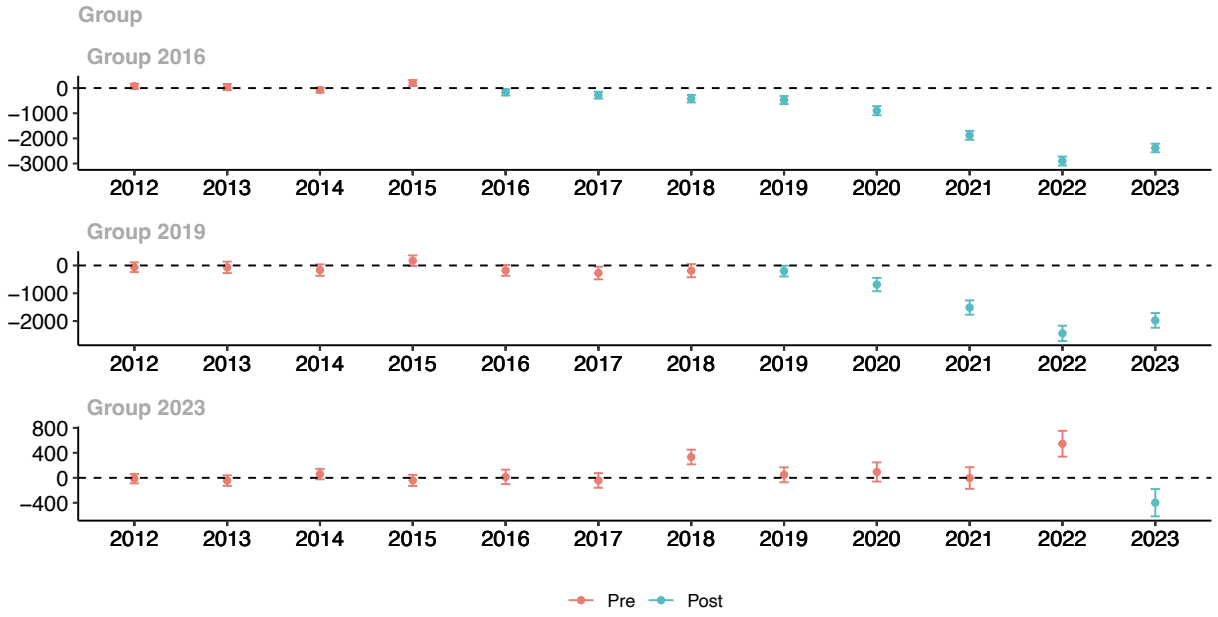


Table B 9. Average Effect by Length of Exposure, Total Annual OOP (event study)

Event time	Estimate	Std. Err.	L 95%	U 95%	Sig
-11	-12.82	24.57	-84.86	59.23	
-10	-43.81	26.59	-121.79	34.17	
-9	60.03	27.34	-20.14	140.20	
-8	-40.82	28.97	-125.77	44.12	
-7	-5.32	32.88	-101.72	91.07	
-6	-48.54	35.45	-152.47	55.40	
-5	200.20	33.32	102.50	297.90	*
-4	79.58	25.03	6.18	152.98	*
-3	26.66	32.14	-67.59	120.90	
-2	-75.28	34.80	-177.31	26.74	
-1	309.81	39.81	193.09	426.53	*
0	**-297.36**	**39.93**	**-414.45**	**-180.28**	*
1	**-450.68**	**42.20**	**-574.43**	**-326.94**	*
2	**-875.18**	**41.78**	**-997.68**	**-752.69**	*
3	**-1294.66**	**48.37**	**-1436.49**	**-1152.83**	*
4	**-1346.89**	**50.02**	**-1493.56**	**-1200.23**	*
5	**-1876.58**	**58.38**	**-2047.76**	**-1705.39**	*
6	**-2900.76**	**60.24**	**-3077.41**	**-2724.12**	*
7	**-2380.75**	**62.45**	**-2563.87**	**-2197.64**	*

Key: Significance noted by * indicates 95% CI does not cross zero; Bolded values indicate post-period

Figure B 2. Average Treatment Effect – Length of Exposure, Total Annual OOP

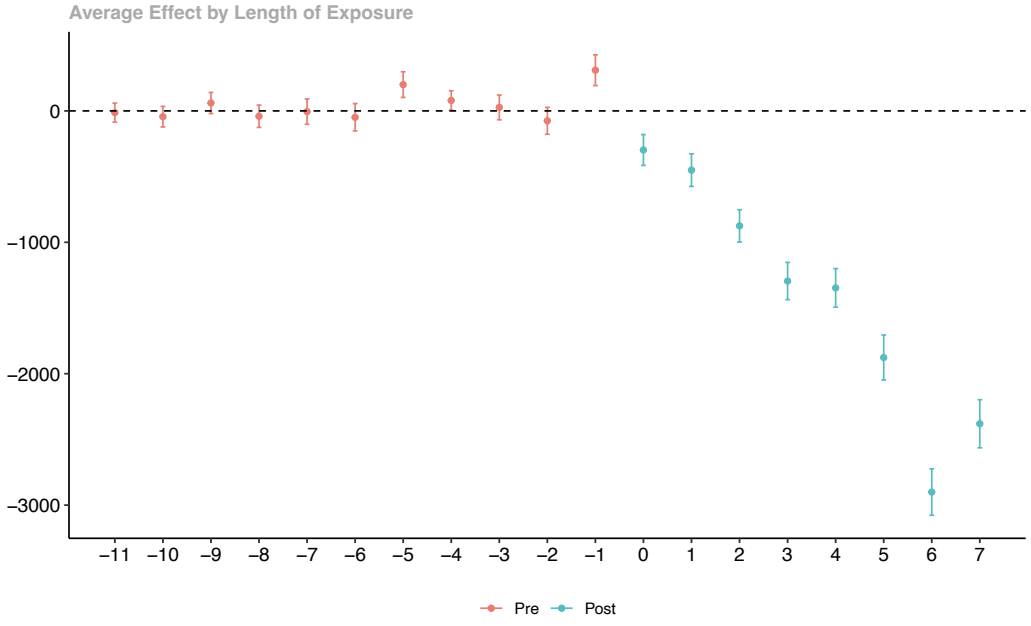
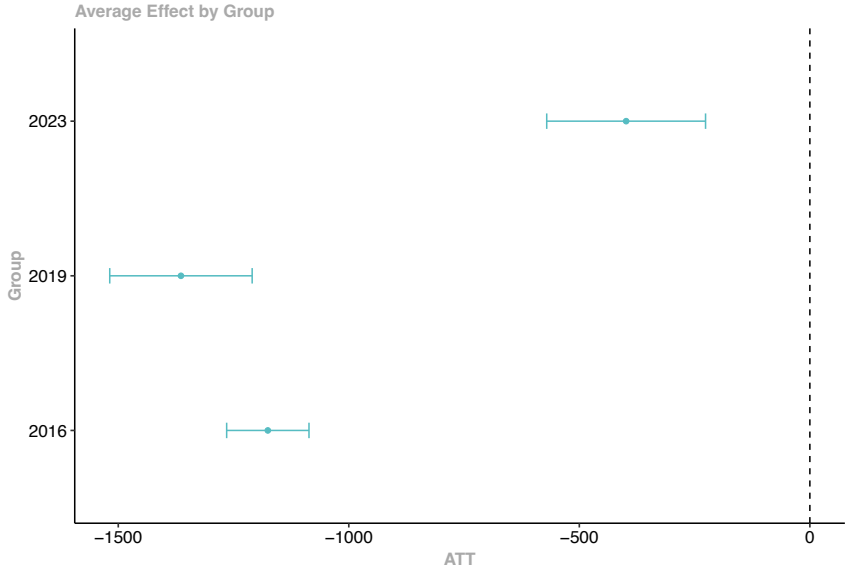


Table B 10. Average Treatment Effect by Group, Total Annual OOP

Group	Estimate	SE	L 95%	U 95%	Sig
Infliximab	-1175.62	37.03	-1264.90	-1086.34	*
Rituximab	-1364.05	64.06	-1518.51	-1209.59	*
Adalimumab	-398.48	71.44	-570.73	-226.22	*

Key: Significance noted by * indicates 95% CI does not cross zero; Group 2018 = infliximab; Group 2019 = rituximab; Group 2023 = adalimumab

Figure B 3. Average Treatment Effect by Group, Total Annual OOP



B6. Robustness Checks

Table B 11. Simple Aggregated Average Treatment Effect

Scenario	ATT	SE	L 95% CI	U 95% CI
Primary Analysis **Control:** Never-treated **Data:** unbalanced panel **Outcome:** Biologic OOP **Anticipation:** 0	-$1104.19	23.47	-$1150.18	-$1058.20
Control: Not-yet-treated **Data:** unbalanced panel **Outcome:** Biologic OOP **Anticipation:** 0	-$1210.68	21.56	-$1252.94	-$1168.41
Control: Never-treated **Data:** unbalanced panel **Outcome:** Biologic OOP **Anticipation:** 1 year	-$1003.65	21.94	-$1046.65	-$960.65
Control: Never-treated **Data:** repeated cross-section **Outcome:** Biologic OOP **Anticipation**: 0	-$1112.89	30.58	-$1172.82	-$1052.96

Table B 12. One Year of Anticipation: Average Treatment Effect, by Group (Biologic OOP)

Drug Group	ATT	SE	L 95% CI	U 95% CI	Sig
Infliximab	-$1059.21	25.46	-$1117.92	-$1000.50	*
Rituximab	-$1519.82	35.57	-$1601.83	-$1437.81	*
Adalimumab	$164.30	69.10	$4.98	$323.63	*