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ORIGINAL RESEARCH ARTICLE

The Price and Market Share Evolution of the Original Biologics and Their Biosimilars in Finland

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Abstract

Background Biological drugs are generally expensive and produce a continuously growing share of drug costs. Yet they are essential in the treatment of many chronic diseases. Biosimilars, clinically equivalent to biological originator products, are expected to restrain drug costs in the biological market.

Objective This study aimed to examine the impact of the biosimilar market entry on the prices of the reference products in outpatient care in Finland, investigate the impact of biosimilar market entries on price competition among biological medicinal products, and examine how the prices and market shares of outpatient biosimilars have developed in Finland during 2009–2020.

Methods This retrospective register study applied data from IQVIA covering national community pharmacy wholesale data between 1 January, 2009, and 31 August, 2020, for somatropin, epoetin, filgrastim, follitropin, insulin glargine, insulin lispro, etanercept, pegfilgrastim, adalimumab, teriparatide, and enoxaparin biosimilars and their reference products, in addition to two relevant insulin products. We determined the monthly wholesale amounts in defined daily doses and wholesale weighted average prices (excluding value-added tax) per defined daily dose for each product. We analyzed the evolution of the price and market shares. We performed a linear segmented regression analysis to examine the impact of the market entry of biosimilars on the prices of reference products.

Results The prices of the reference products mainly decreased after the biosimilar entered the market. If the reference product price was not reduced, it was no longer reimbursable after evaluation under the Health Insurance Act, leading to marginal market shares. The changes in the prices of biosimilars were not as remarkable as the changes in the prices of reference products after the biosimilar market entry. For most active substances, biosimilar prices were stable or decreased. The utilization of biosimilars varied widely between different active substances at the end of the observation period.

Conclusions Changes in pricing policy and the public reimbursement scheme related to the market entry of biosimilars were the main reasons for the decrease in the prices of reference products. Therefore, biosimilars did not generate genuine price competition between biological products. In many of the drug groups examined, the market shares of biosimilars have growth potential in the future.

1 Introduction

Global pharmaceutical costs continue to rise, and spending on medicines is expected to increase at an annual rate of 3–6% [1]. A significant part of pharmaceutical costs is

Key Points

The price of the reference product decreases after the biosimilar market entry, but current initiatives do not support genuine price competition between biosimilars and reference products.

Biosimilars still have a minor market share among some of the biologics, and they have significant growth potential in the market in the future.

Biosimilar prices remained stable or decreased after the market entry.

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caused by the sale of biological medicinal products (biologics): for example, over 30% of drug spending is driven by biologics in Europe [2]. Biologics are essential in treating many chronic diseases such as diabetes mellitus, autoimmune diseases, and cancers [3].

A biosimilar is a biological medicinal product highly similar to another biological medicinal product ('reference medicine') already having a market approval in the European Union [3]. Biosimilars are expected to lead to significant cost savings in the biologics market [1]. Because of more affordable development costs, a biosimilar may enter the market at a lower price than its reference product once the patent and marketing protection of the reference product has expired [3]. The introduction of biosimilars may also lower the prices of reference products [4].

In Finland, biologics are dispensed by two routes with separate funding mechanisms. In hospitals, most administered biologics are intravenous and/or monoclonal antibodies for anti-cancer treatments [5]. The majority of the self-injectable biologics are reimbursable and dispensed from the community pharmacies for outpatient care. The prices of reimbursable biologics are highly regulated. Under the Ministry of Social Affairs and Health, the Pharmaceuticals Pricing Board sets the maximum wholesale prices for reimbursable medicinal products in outpatient care [6]. The retail prices of the reimbursable prescription medicines are based on maximum wholesale prices, whereas pharmaceutical companies can freely set the price of non-reimbursable medicines. The prices of prescription medicines are the same in all Finnish community pharmacies. Two supply-side changes in pharmaceutical legislation in 2013 and 2017 have had a significant impact on the maximum wholesale prices of biologics in Finland. First, in 2013, the wholesale prices of all medicines outside the reference price system were reduced by 5% [7]. Second, in 2017, two amendments regarding biosimilars were added to the Health Insurance Act (2004/1224) [6]. According to the amendments, the first biosimilar entering the market must be priced at least 30% lower than the reference product to gain reimbursable status. Further, when a biosimilar product containing the same active substance enters the reimbursement system, the Pharmaceuticals Pricing Board is required to re-evaluate the reasonable wholesale price for the reference product [6]. In the only demand-side regulation, which came into force in 2017, the prescriber must choose the most affordable comparable product if a biosimilar is available for biological medicine [8]. To date, biologics are not substituted in community pharmacies in Finland [9].

Despite policy and legislative changes, the increase in costs has continued in the Finnish prescription pharmaceutical market in outpatient care [10]. In 2020, sales of outpatient prescription drugs, measured at retail prices including value-added tax, increased 2.1% compared with the previous year, EUR 2.33 billion of the total drug sales of EUR 3.52 billion. A significant part of the growth is caused by the sale of biologics [11]. The objective of this study was to find out what impact the market entry of biosimilars has on the prices of the reference products in outpatient care in Finland and to investigate whether biosimilars trigger price competition for biologics. In addition, the study examined how the prices and market shares of outpatient biosimilars have developed in Finland from 2009 to 2020.

2 Methods

2.1 Selection of Included Biological Medicinal Products and Data

The study included all the biological medicinal products with biosimilars on the market sold between 1 January, 2009 and 31 August, 2020, in community pharmacies in Finland (Table 1) limiting the data to the outpatient care prescription drug market. Additionally, two relevant insulin products (Toujeo® and Liprolog®) containing the same active substances as included reference products and biosimilars were included. These products were included to test whether competitors with the same active substance would impact the market development of the insulin biosimilars. Toujeo® is an improved version of the insulin glargine reference product containing three times more insulin glargine than the reference product [12], and Liprolog® is an insulin lispro product with the same marketing authorization holder as the insulin lispro reference product [13].

In Finland, the prices of outpatient prescription drugs are publicly available, but product-specific wholesale data are not. The data for the study were obtained from IQVIA (formerly IMS Health and Quintiles), which has collected data on pharmacy wholesale sales of medicines in Finland since 2009. The data were collected based on Anatomical Therapeutic Chemical codes from Finnish pharmacy wholesale data at the product level. The observation period began on 1 January, 2009, for the products for which the first biosimilar entered the market before 1 January, 2012. For the other products, the observation period started 3 years before the first biosimilar of the active substance entered the market. The observation period continued for all included products until 31 August, 2020. The monthly updated data of Anatomical Therapeutic Chemical code, Nordic product number, trade name, package description (package size, strength, dosage form), number of packages sold, and wholesale value (excluding value-added tax) for the included medicinal products (Table 1) were received.

Table 1 Included biological medicinal products and their biological medicine status grouped by active substances, ATC codes, and therapeutic areas being listed by the date of the first biosimilar entered the Finnish market before August 2020 [14–17]

ATC code	Active substance	Trade name	Biological medicine status	Market entry in Finland	Examples of therapeutic areas
H01AC01	Somatropin	Genotropin®	Originator	1 February 1994	Growth hormone deficiency
		Omnitrope®	Biosimilar	15 November 2007	
B03XA01	Epoetin alfa/zeta	Eprex®	Originator	1 March 1991	Anemia
		Retacrit®	Biosimilar	1 August 2008	
		Binocrit®	Biosimilar	1 November 2008	
L03AA02	Filgrastim	Neupogen®	Originator	22 August 1991	Neutropenia
		Ratiograstim®	Biosimilar	1 May 2009	
		Zarzio®	Biosimilar	15 January 2010	
		Nivestim®	Biosimilar	16 August 2010	
		Accofil®	Biosimilar	15 August 2015	
G03GA05	Follitropin alfa	Gonal-F®	Originator	15 May 1997	Infertility
		Bemfola®	Biosimilar	15 September 2014	
		Ovaleap®	Biosimilar	21 May 2020	
A10AE04	Insulin glargine	Lantus®	Originator	15 May 2003	Diabetes mellitus
		Lantus Solostar®	Originator	1 November 2007	
		Toujeo®	Other	1 July 2015	
		Abasaglar®	Biosimilar	1 November 2015	
A10AB04	Insulin lispro	Humalog®	Originator	1 July 1996	Diabetes mellitus
		Humalog Kwikpen®	Originator	1 December 2008	
		Insulin Lispro Sanofi®	Biosimilar	1 January 2018	
		Humalog Junior Kwikpen®	Originator	1 April 2018	
		Liprolog®	Other	10 May 2019	
L04AB01	Etanercept	Enbrel®	Originator	2 April 2007	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis, juvenile rheumatoid arthritis
		Erelzi®	Biosimilar	1 February 2018	
L03AA13	Pegfilgrastim	Neulasta®	Originator	31 December 2002	Neutropenia
		Pelgraz®	Biosimilar	15 October 2018	
		Ziextenzo®	Biosimilar	1 October 2019	
		Pelmeg®	Biosimilar	15 November 2019	
		Fulphila®	Biosimilar	1 July 2020	
L04AB04	Adalimumab	Humira®	Originator	1 March 2004	Rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, uveitis, hidradenitis suppurativa, ulcerative colitis, Crohn's disease
		Amgevita®	Biosimilar	15 November 2018	
		Hyrimoz®	Biosimilar	1 December 2018	
		Hulio®	Biosimilar	15 December 2018	
		Idacio®	Biosimilar	1 January 2020	
H05AA02	Teriparatide	Forsteo®	Originator	28 July 2003	Osteoporosis
		Movymia®	Biosimilar	15 September 2019	
B01AB05	Enoxaparin sodium	Klexane®	Originator	4 April 1991	Venous thromboembolism
		Inhixa®	Biosimilar	1 January 2020	
		Enoxaparin Becat®	Biosimilar	15 January 2020	
		Ghemaxan®	Biosimilar	15 April 2020	

ATC code Anatomical Therapeutic Chemical code

2.2 Data Analysis

2.2.1 Data Processing

We performed data processing and analysis of the market share and price evolution with Microsoft Office Excel. Parallel import products were included with the same trade name, as parallel imported products comprise only a small share of wholesale sales in Finland [11]. We determined the amount of the active substance in each package by the package description or by using a Nordic product number from FimeaWeb, a pharmaceutical product database provided by the Finnish Medicines Agency Fimea [16]. The consumption of active substances was measured as defined daily doses (DDDs), which refers to the presumed average adult maintenance dose per day when a drug is used for its primary indication [18]. We used the year 2020 DDD values [19]. The total monthly consumption of the products (in DDDs) comprised all products with the same trade name. In addition, we combined the monthly consumption of the reference product and its biosimilars for each active substance.

We used the monthly wholesale weighted average price per DDD to describe drug prices. It was calculated for each included product. A common weighted average price for biosimilars was calculated for those active substances with more than one biosimilar. All prices were converted to 2018 Euros.

2.2.2 Analysis of Market and Price Evolution

The evolution of market shares and the wholesale prices of the included products were presented graphically with subsequent analysis of their utilization and price evolution. The results were synthesized with reimbursement information and the reimbursement expiry dates for the products obtained from the databases of Finnish authorities or official notifications/notices [20–23]. For the active substances, for which the first biosimilar entered the market after 1 January 2012, the reference product price evolutions were summarized in a graph. The price of the reference product was presented in relation to its price at the moment of its first biosimilar market entry.

2.2.3 Statistical Analysis

The effect of the biosimilar market entry on the price of the reference product was estimated by an interrupted time series analysis, which is a strong quasi-experimental design to study the long-term effects of interventions over time [24]. We used a segmented linear regression analysis, which can be used to model an interrupted time series analysis and to estimate the effects of interventions on the variable under study. This method allows the changes in trends and levels to be analyzed by comparing the values of the variables before and after the intervention. The interrupted time series analysis has previously been used together with a segmented linear regression analysis (see, e.g., Koskinen et al. [25, 26]).

The time series can be divided into two or more segments at the change points in the series [24]. In the current study, we divided the time series for each active substance into two parts. The time series was interrupted from the moment the decrease in the price of the reference product was seen graphically. If no change in the price was observed, the time series was interrupted when the biosimilar entered the market. This approach was chosen assuming that the price change of the reference product was because of the biosimilar market entry (considered as an intervention). However, we were unable to foresee when this change would occur. Regression analysis was performed for reference products for which the first biosimilar was introduced after 1 January, 2012. The statistical analysis was carried out with the R program (version 1.3.1093).

Two regression models were used in this study. The best-fitting model for each active substance was determined by an analysis of variance and comparison of the Akaike Information Criterion and Bayesian Information Criterion values (described, for example, by Kuha [27]). If the Akaike Information Criterion and Bayesian Information Criterion values were inconsistent, the model was selected based on the Akaike Information Criterion value and the analysis of variance. In the first model, the explanatory factors were time and the market entry of the biosimilar. Model 1 takes the form of Equation 1:

$$Y_t = \beta_0 + \beta_1 \times \text{time} + \beta_2 \times \text{intervention}_t + \varepsilon_t,$$

where Y_t is the average wholesale price per DDD of the reference product in month t, β_0 estimates the baseline level of the average wholesale price per DDD of the reference product per month at time zero, β_1 estimates the monthly baseline trend of the average wholesale price per DDD of the reference product before interruption, *time* is a continuous variable indicating time in months from the start of the observation period starting from zero, β_2 estimates the level change in the average wholesale price per DDD of the reference product immediately after the time series interruption, intervention_t indicates time t and gets a value of 0 before and a value of 1 after the interruption, and ε_t is the error term.

The second model explained the price by time, biosimilar market entry, and a parameter describing the change in trend. Model 2 takes the form of Equation 2:

$$Y_t = \beta_0 + \beta_1 \times \text{time} + \beta_2 \times \text{intervention}_t + \beta_3 \times \text{timeafterintervention} + \varepsilon_t,$$

where the parameters are otherwise the same as in Model 1, but β_3 and *time after intervention* are added. β_3 estimates the

monthly change in the trend of the average wholesale price per DDD of the reference product after the interruption, compared with the monthly trend before the interruption and *time after intervention* is a continuous variable expressing the time in months after the interruption and receives the value 0 before the interruption.

We used the Durbin–Watson test [28] and the Newey–West method [29] because of the possible autocorrelation of the time series analysis. In addition to the autocorrelation, the Newey–West method takes heteroskedasticity into account. The results are autoregressively corrected results and presented with a significance level of 0.01.

3 Results

3.1 Market Share Evolution of Biosimilars

The biosimilar uptake varied between different active substances (Table 2, Electronic Supplementary Material [ESM]). At the end of the observation period in 2020, the market shares of filgrastim and epoetin biosimilars were 100%, while the market shares of insulin glargine (6%), teriparatide (0%), and enoxaparin (6%) biosimilars were low. The biosimilar market shares for the other seven active substances were in-between.

The combined utilization of the reference product and its biosimilars, measured by DDDs, was the highest for insulin glargine, followed by enoxaparin, adalimumab, insulin lispro, and etanercept at the end of the observation period. The sales of the first biosimilars of these five active substances started in the first month when entering the market (Table 2). Biosimilars for other active substances that entered the market during the observation period were not sold during the first month. Six active substances had multiple biosimilars on the market during the observation period. The first biosimilar of the active substance had the largest market share by the end of the observation period, except filgrastim, whose second biosimilar had the largest market share.

Non-biosimilar competitors Toujeo® and Liprolog® had gained remarkable market shares (32% and 49%, respectively) at the end of the observation period (Table 2, ESM). After their introduction to the market, competitors' uptakes were the same or more efficient than biosimilar uptake of the same active ingredient.

3.2 Price Evolution of Biosimilars

Seven of the first biosimilars were 26–31% lower priced than the reference product when the biosimilar was first sold (Table 2, ESM). The first biosimilar of the insulin glargine had the smallest price difference to the reference product (15%), and the first biosimilar of enoxaparin had the largest (42%). For all active substances, apart from enoxaparin, biosimilar prices either remained steady or decreased over the observation period from 1 January, 2009 (somatropin and epoetin) or the first biosimilar market entry (other active substances) to 31 August, 2020. The combined wholesale weighted average price of enoxaparin biosimilars increased by 22%.

Somatropin, insulin glargine, insulin lispro, etanercept, and teriparatide had only one biosimilar on the market during the observation period (Table 2). The prices of these biosimilars had only small changes, except the somatropin biosimilar, whose price decreased by 27% in September 2010 (ESM). Only small changes were observed in the prices of the two biosimilars of follitropin during the observation period. However, the first of two epoetin biosimilars had more price variation (ESM). The price of the epoetin first biosimilar slowly increased but began to decrease in October 2012. After that, the price has slightly decreased or stayed stable. Filgrastim, pegfilgrastim, adalimumab, and enoxaparin had more than two biosimilars on the market. The prices of the filgrastim biosimilars began to differ in 2017 when the prices of the biosimilars either stayed stable or decreased (maximum price decrease 63%). The price of the pegfilgrastim first biosimilar decreased by 14%, and the third biosimilar by 7% over the observation period. The price development of the pegfilgrastim second and fourth biosimilars is unknown because these products were not sold over the observation period, and we could not calculate the wholesale weighted average price. The prices of the first three adalimumab biosimilars decreased by 19–23%, and the fourth biosimilar price stayed stable.

For all active substances for which prices of biosimilars and reference products were known at the end of the observation period, biosimilars were more affordable than reference products. However, the insulin lispro competitor Liprolog® was sold at a lower price than the insulin lispro biosimilar.

3.3 Effect of the Biosimilar Market Entry on the Price of the Reference Product

There were only small changes in the price of the somatropin reference product after the biosimilar market entry, except at the beginning of the year 2013 (62 months after the biosimilar market entry) when the price decreased approximately 30% (ESM). The largest price decrease for the epoetin reference product was 12% in October 2009, and after that, the price has slightly increased or stayed stable. The price of the filgrastim reference product seemed to decrease 43 months after the biosimilar market entry in January and February 2013. However, after 2 years, the price increased even to a higher level than before the price decreased. At the end

Table 2 Summary of the uptake and utilization of biosimilars and their price differences to the reference products in Finland during the observation period from 1 January 2009 (somatropin and epoetin) or the first biosimilar market entry (other active substances) to 31 August 2020 [20–23]

Active substance	The market share of biosimilars in the market that included biosimilars and the reference product at the end of the observation period	The biosimilar market share distribution at the end of the observation period				The price difference between the reference product and the first biosimilar when the biosimilar entered the market	The price difference between the reference product and biosimilars at the end of the observation period	The reimbursement status for the reference product at the end of the observation period	The biosimilar was sold in the first month it entered the market
		First	Second	Third	Fourth				
Somatropin	73%	73%				–[d]	3%	Yes	–[j]
Epoetin	100%	100%	0%[c]			–[d]	–[g]	No (the reimbursement has ended on 31 March, 2011)	–[j]
Filgrastim	100%	3%	69%	24%	5%	30%[e]	–[g]	No (the reimbursement has ended on 31 March 2013)	No
Follitropin	24%	23%	0%			30%[e]	10%	Yes	No
Insulin glargine	6% (4%[a])	6%				15%	1%	Yes	Yes
Insulin lispro	99% (51%[b])	99%				26%[f]	28%	No (the reimbursement has ended on 31 May 2019)[i]	Yes
Etanercept	30%	30%				30%	12%	Yes	Yes
Pegfilgrastim	38%	37%	0%	1%	0%	30%[e]	6%	Yes	No
Adalimumab	35%	18%	11%	5%	1%	30%	22%	Yes	Yes
Teriparatide	0%	0%				31%[e]	–[h]	Yes	No
Enoxaparin	6%	6%	0%	0%		42%	28%	Yes (the reimbursement is ending on 30 November 2020)	Yes

[a]The market share of the biosimilar on the market, including also Toujeo®

[b]The market share of the biosimilar on the market, including also Liprolog®

[c]The biosimilar is no longer on the market

[d]The observation period started later than the market entry of the biosimilar, thus the price difference is unknown

[e]The biosimilar was not sold in the first month after the market entry. The wholesale weighted average price of the biosimilar in its first sale month as compared to the price of the reference product at the time when biosimilar entered the market

[f]The price difference is not at least 30% because we used the wholesale weighted average price, which considers all different packages sold under the same trade name. If the pen package of the biosimilar is compared to the pen package of the reference product (not included in the analysis), the price difference was 30%

[g]The reference product was not sold at the end of the observation period, thus the wholesale weighted average price for the reference product could not be determined

[h]The biosimilar was not sold at the end of the observation period, thus the wholesale weighted average price for the biosimilar could not be determined

[i]Some of the products were no longer reimbursed after 30 September 2018

[j]The observation period started later than the market entry of the biosimilar, thus it is unknown whether biosimilar was sold or not

of the observation period, epoetin and filgrastim reference products were no longer reimbursed (Table 2).

The relative changes in the wholesale weighted average prices of the reference products were further analyzed for the eight other active substances (Fig. 1). For enoxaparin, teriparatide, insulin lispro, adalimumab, and etanercept, the price of the reference product remained fairly stable before the biosimilar entered the market. For insulin glargine, pegfilgrastim, and follitropin, the price of the reference product was higher 3 years before the biosimilar market entry compared to the price at the time of the biosimilar market entry.

Compared to the time before biosimilars entered the market, larger changes in prices of the reference products were observed after the biosimilar market entry (Fig. 1). For all active substances, except enoxaparin and insulin lispro, the price of the reference product decreased permanently after the biosimilar entered the market. With enoxaparin, whose observation period was 8 months after biosimilar introduction, no changes in the price of the reference product were observed. The price of the insulin lispro reference product decreased at first, but after 18 months, it increased higher than at the time of biosimilar introduction. At the end of the observation period, the insulin lispro reference product was no longer in the reimbursement scheme (Table 2).

For those active substances whose biosimilars entered the market after 2017, the prices of the reference products fell shortly after the biosimilars entered the market compared with the price decreases for insulin glargine and follitropin (Fig. 1). The insulin glargine reference product price decreased in December 2016 and again in April 2017. The follitropin reference product price decreased between March and June 2017.

Model 2 was a better fit for seven reference products in the statistical analysis. Model 1 was only used for the teriparatide reference product. The changes in the price level of the reference products after the interruption (the price decrease of the reference product or biosimilar market entry) were statistically significant for six reference products (follitropin, insulin glargine, pegfilgrastim, adalimumab, teriparatide and enoxaparin) and statistically insignificant for two reference products (insulin lispro and etanercept) (Table 3). The change in the price level of the etanercept reference product after the interruption was not statistically significant, although the price drop can be seen in Fig. 1. However, without the Newey–West method [29], the change in the price level was a significant result ($p < 0.001$), and similarly, Model 1 yielded a statistically significant result ($p < 0.001$) using the Newey–West method. There were statistically significant price trends of the reference products before the interruption of the time series and statistically significant changes in the price trends of the reference products after the interruption of the time series (Table 3).

4 Discussion

In light of the global need to increase price competition among interchangeable biologics, our study provides several findings on the price and market share evolution of the original biologics and their biosimilars on a national level. Our study shows that the biosimilar market entry reduces the prices of reference products in outpatient care in Finland. However, the price reduction of the reference products can be seen as a consequence of the pricing policy and public

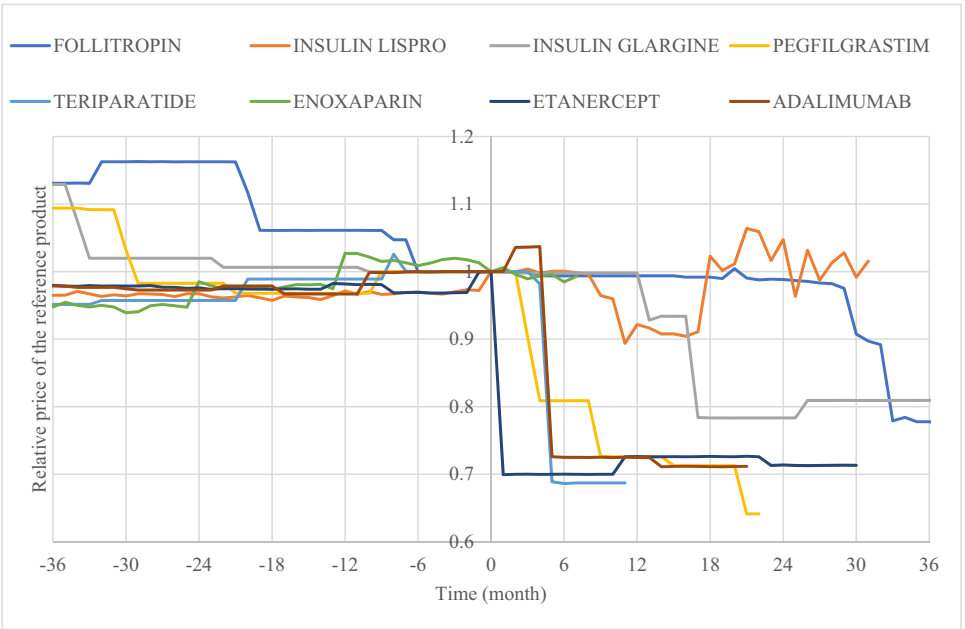

Fig. 1 Development of relative prices of reference products for eight active substances. The observation period began 3 years (36 months) before the first biosimilar entered the market and continued for 3 years (36 months) thereafter. The relative prices of the reference products are standardized to be 1 when the first biosimilar entered the market (at 0 months). The price decreases for insulin glargine (− 33 months) and follitropin (− 19 months) reference products occurred in 2013

Table 3 Impact of biosimilar market entry on the reference product price (in Euros) per DDD. Active substances are listed by the date the first biosimilar entered the Finnish market. Results are presented with a 95% confidence interval, and statistically significant p values ($p < 0.01$) are bolded

Active substance	Compared to time series interruption	Estimate (€/DDD)	95% CI (€/DDD)	p value
Follitropin	Level before (β_0)	28.269	26.376; 30.161	**<0.001**
	Trend before [per month] (β_1)	− 0.078	− 0.122; − 0.034	**<0.001**
	Level change after (β_2)	− 3.254	− 4.539; − 1.970	**<0.001**
	Trend change after [per month] (β_3)	0.086	− 0.002; 0.174	0.055
Insulin glargine	Level before (β_0)	1.270	1.241; 1.298	**<0.001**
	Trend before [per month] (β_1)	− 0.001	− 0.002; − 0.001	**0.003**
	Level change after (β_2)	− 0.185	− 0.283; − 0.086	**<0.001**
	Trend change after[(per month] (β_3)	0.001	− 0.002; 0.004	0.503
Insulin lispro	Level before (β_0)	0.749	0.740; 0.759	**<0.001**
	Trend before [per month] (β_1)	0.001	0.000; 0.001	0.048
	Level change after (β_2)	− 0.054	− 0.095; − 0.013	0.011
	Trend change after [per month] (β_3)	0.004	0.001; 0.006	**0.006**
Etanercept	Level before (β_0)	31.279	31.092; 31.465	**<0.001**
	Trend before [per month] (β_1)	− 0.000	− 0.016; 0.016	0.989
	Level change after (β_2)	− 8.725	− 21.699; 4.250	0.184
	Trend change after [per month] (β_3)	0.021	− 1.069; 1.112	0.969
Pegfilgrastim	Level before (β_0)	44.290	41.183; 47.398	**<0.001**
	Trend before [per month] (β_1)	− 0.078	− 0.210; 0.054	0.241
	Level change after (β_2)	− 5.646	− 8.150; − 3.142	**<0.001**
	Trend change after [per month] (β_3)	− 0.327	− 0.513; − 0.141	**<0.001**
Adalimumab	Level before (β_0)	32.331	31.857; 32.805	**<0.001**
	Trend before [per month] (β_1)	0.039	0.011; 0.067	**0.007**
	Level change after (β_2)	− 9.460	− 10.403; − 8.517	**<0.001**
	Trend change after [per month] (β_3)	− 0.080	− 0.113; − 0.047	**<0.001**
Teriparatide	Level before (β_0)	10.254	10.155; 10.354	**<0.001**
	Trend before [per month] (β_1)	0.016	0.012; 0.020	**<0.001**
	Level change after (β_2)	− 3.544	− 3.706; − 3.382	**<0.001**
Enoxaparin	Level before (β_0)	1.499	1.481; 1.517	**<0.001**
	Trend before [per month] (β_1)	0.004	0.003; 0.005	**<0.001**
	Level change after (β_2)	− 0.043	− 0.065; − 0.021	**<0.001**
	Trend change after [per month] (β_3)	− 0.007	− 0.008; − 0.006	**<0.001**

CI confidence interval, *DDD* defined daily dose

reimbursement scheme concerning the market entry of the first biosimilars. Biosimilar prices usually remained stable or decreased during the observation period depending on the number of competing biosimilars. The market shares of biosimilars were relatively minor compared with the market shares of the reference products, with significant variations between different active substances.

The changes in pharmaceutical pricing and reimbursement legislation in 2013 [7] and 2017 [6] impacted the prices of the included products in this study. These two changes seem to explain almost all reference product price changes being more than the annual variation in the price indexes. For all products (reference products and biosimilars) whose observation periods were started before 2013, a single decrease in prices was observed in 2013. Otherwise, the reference product prices mainly stayed stable before the biosimilar introduction to the market. Price trends were generally marginal and comparable to the annual variation in the price index. Before 2017, the market entries of biosimilars were not found to cause immediate price reductions for the reference products. Following the mandatory price regulation in 2017, the decline in the prices of reference products occurred relatively soon after the first biosimilar entered the market, and the price generally decreased only once. After that, the changes in the price trends of the reference products were mainly minor. Similar results from the price decrease of the reference product after the biosimilar market entry have also been reported previously in Finland

and other European countries [30, 31]. However, this study did not observe permanent price decreases for insulin lispro, filgrastim, epoetin, and enoxaparin reference products. As a result, the first three of these reference products were no longer covered by the public reimbursement scheme at the end of the observation period [23]. Subsequently, the latter reference product was re-evaluated and not reimbursed after the end of November 2020 [22].

Although the reference product price reduction is mainly because of price regulation, the biosimilar market entry enables the treatment of patients with more affordable biologics. However, the savings may not be gained if the patient's medication is switched to another competitor, such as an improved version or a follow-on drug (a compound with a very similar mechanism of action, which usually does not add therapeutic value to medicines already on the market [32]). We observed that the improved competitor of the insulin glargine gained a significant market share after entering the market. A recent study on the Finnish pharmaceutical market showed that some patients treated earlier with a reference product were switched to improved versions after the biosimilar market entry [11].

In this study, the biosimilar prices mainly remained steady or decreased over a long observation period, starting from the market entry of the first biosimilar for each active substance until 31 August, 2020. The price regulation of reimbursable biologics was seen from 2017. After that, the first biosimilar to be reimbursed must be at least 30% lower priced than the reference product [6]. In addition, the prices of subsequent biosimilars entering the market must be at least as low as the price of the first biosimilar. We found that if there were more than two biosimilars on the market, introducing new biosimilars triggered a slight price reduction among the previous biosimilars. This finding may indicate that one or two biosimilars on the market do not yet lead to price competition between interchangeable products. However, further research is needed to confirm this finding.

The mandatory price reduction of the reference product may curb incentives to switch to biosimilars and lead to meager use of biosimilars in the future. This situation may not be a problem, but mandatory price reductions for reference products may hinder long-term competition by limiting price differences between products and affecting incentives to enter the market for biosimilar products [30, 33]. Incentives for pharmaceutical companies to bring biosimilars to the market may weaken if biosimilars do not achieve reasonable market shares. The most significant market shares were for epoetin, filgrastim, and insulin lispro biosimilars at the end of the observation period in 2020, considering the overall market for the reference product and its biosimilars. However, the utilization of biosimilars varies greatly between different biological agents, and the uptake is still scarce among some active substances. The lowest biosimilar market shares were for enoxaparin and teriparatide with the shortest observation periods and insulin glargine. Similar variation in biosimilar use has been observed between active substances elsewhere in Europe [2]. Several studies have explored initiatives and policies that may influence biosimilar uptake [34–37]. In Finland, the biosimilar uptake has been promoted by legislative changes in public reimbursement schemes and prescribing rules and information guidance targeted mainly at physicians [38]. However, our study confirms that although Finnish prescribers have positive views on biosimilars [39], these initiatives have not been effective enough in promoting biosimilar uptake as the reference product had the highest market share at the end of the observation period in several active substances. Therefore, Finland should consider new, more effective methods to incite biosimilar uptake and trigger price competition [39, 40].

The strengths of this study were the use of comprehensive nationwide data and the application of a robust scientific method suitable to analyze the impact of the interventions on the biologics market in outpatient care. In addition, we had a long observation period that covered almost the entire time biosimilars have been on the Finnish market. To the best of our knowledge, no previous comprehensive nationwide analysis on this topic has been published from the Western markets. However, our study has some limitations. First, we excluded the competitors of biosimilars, such as improved versions and follow-on products from the study, except for two insulin products. Competitors with the same or a similar mechanism of action may impact the biosimilar market development. This perspective should be considered in pharmacoeconomic studies focusing on one or a few indications treated by a biological medicine or its competitors. For the complete nationwide data used in the present study, extended inclusion criteria were not applicable. Further, the effect of competitors should be noted as a potential bias in the statistical analysis. A reference product's price change could have been due to the market entry of any competitor and not specifically due to a biosimilar, as assumed in our approach. However, the graphs of the market shares and price evolutions in the ESM support our assumptions. Second, we made some extrapolations using wholesale data and wholesale weighted average prices instead of retail sales in community pharmacies. However, as the prices of biologics are relatively high, it can be assumed that community pharmacies are hesitant to store many expensive medicines and the use of wholesale data is representative. In addition, the sales prices of prescription medicines are the same in all Finnish community pharmacies based on wholesale prices. The use of the wholesale weighted average price may skew the prices if the monthly wholesale is minor and targeted

to small package sizes. We also used DDDs in the study, which describe the presumed average adult maintenance dose per day when a drug is used for its primary indication [18]. These are not necessarily equal to the prescribed doses of the drug for patients. However, DDDs can be used to compare drug utilization regardless of different strengths or package sizes between products and active ingredients. Additionally, the use of DDDs and Anatomical Therapeutic Chemical codes enables the international comparison of the results [41] increasing the generalizability of our findings. However, the national context should be noted as the policies for biosimilar uptake vary across Europe [35].

5 Conclusions

The market entry of biosimilars induced a reduction in the prices of the reference products in outpatient care in Finland. However, the prices of the reference products decreased mainly because of the public reimbursement legislation. Therefore, biosimilars did not create genuine price competition between the biosimilar and the reference product. The market shares of biosimilars have further growth potential in the Finnish pharmaceutical market.

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Declarations

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Availability of data and material The data that support the findings of this study are available from IQVIA, but restrictions apply to the availability of these data as they are not publicly available. However, data are available from the authors upon reasonable request and with the permission of IQVIA.

Code availability The code is available from the authors upon reasonable request.

Authors' contributions All authors contributed to the study conception and the design of the data evaluation, analysis, and interpretation. Data analysis was performed by SVL. The first draft of the manuscript was written by SVL and HMT, and all authors critically revised the previous versions of the manuscript. All authors read and approved the final manuscript.

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