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Initial prescriptions and medication switches of biological products: an analysis of prescription pathways and determinants in the Swiss healthcare setting

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ABSTRACT

Objectives Biological products have contributed to extraordinary advances in disease treatments over the last decade. However, the cost-saving potential of imitator products, so-called biosimilars, is still underresearched in Switzerland. This study aims to assess biosimilars' prescriptions at treatment initiation and their determinants, as well as biological therapy switches.

Design We analyzed longitudinal data for biosimilar prescriptions in Switzerland using descriptive statistics and logistic regression to quantify the associations with individual, pharmaceutical, and provider-related variables.

Setting The analysis is based on de-identified claims data of patients with mandatory health insurance at Helsana, a leading Swiss health insurance.

Participants Overall, 17'654 patients receiving at least one biological product between 2016 and 2021 were identified.

Primary and secondary outcome measures: We differentiated between initial prescriptions and follow-up prescriptions. Our regression focused on initial prescriptions due to evidence indicating that patients tend to follow the medication prescribed at therapy initiation.

Results Although biosimilars market share was low (28.6%), the number of prescriptions has increased. Few medication switches were detected. Increased relative price difference was associated with decreased probability of biosimilar prescriptions, whereas male sex, an increase of available imitator drugs on the market and, larger packaging sizes, and prescriptions from specialists or physicians in outpatient settings were associated with increased biosimilars use.

Conclusion The low number of biosimilar prescriptions despite the proliferating biosimilar market indicates a high potential for biosimilar diffusion. Our research highlights the need for awareness initiatives to improve understanding among patients and physicians, enabling informed, shared decision-making about biosimilar prescriptions.

[249 of max 250 words]

Key words: biosimilars, biologics, reference products, switches, initial prescription

ARTICLE SUMMARY

Strengths and limitations of this study:

- First scientific study to evaluate the prescription of biosimilars using a comprehensive set of sociodemographic, pharmaceutical, and healthcare provider variables representing a nearly representative database in Switzerland.
- This research paper is the first to divide the medication treatment pathway into initial and follow-up prescriptions, with a specific focus on the initial prescriptions. This is particularly relevant, as initial prescriptions often influence subsequent prescribing decisions as patients are less willing to switch biological medication therapy.
- This study was the first to assess determinants of initial prescriptions in the context of biosimilars.
- Some demand-related factors (patients' health status, beliefs, and experiences) and supply-related factors (physicians' incentives and beliefs) about biosimilars could not be accounted using the claims data.

BACKGROUND

Biological products increased the spectrum of available treatment options considerably in the treatment of many cancers and autoimmune diseases. However, these medications are more expensive compared to many conventional synthetic drugs as they are produced by living cells and, thus, require a more complex manufacturing process. Currently, there are a considerable number of biologics in the final stages of development and approval [1, 2]. The healthcare systems are likely to incur substantial costs even if just a small proportion of these biologics is

granted market approval. One lever to curb rising drug costs is the replacement of biologics after patent expiration with less expensive imitator products, also known as biosimilars. Due to the biotechnological manufacturing process, exact copies of the biological products are not achievable. As a result, minor structural deviations in the biosimilar are unavoidable [3, 4], and regulatory authorities accept them for market approval [5, 6].

In Switzerland, a Swiss report has estimated a cost saving potential of over 60 million Swiss francs for the complete replacement of reference products with biosimilars in 2019 [7]. In the coming years, cost saving potential will increase as several top-selling biologics will lose their patent protection in Switzerland [7, 8] and corresponding biosimilars have already been approved in the European Union (EU) [2, 9, 10]. However, the realization of the cost saving potential us is assumed to be curbed because of skepticism about biosimilars from both the patient and physician side [11–14]. At the same time, patients and their health care providers seem to be less willing to switch biological products when therapy has already been started [15]. Consequently, the choice of initial prescription (IP) at therapy initiation is the decisive factor for following medication prescriptions. Despite the significant role of IP in shaping subsequent treatment pathways, research on the prescription behavior of biological products at therapy initiation and the impact of IP is limited. Existing studies have only demonstrated that patients tend to remain on their initial biological treatment product once medication treatment has been initiated. Thus, there is a need for further investigation into the influencing factors of IP and their influence on the choice of medication path. Thus, this study aims to assess biosimilars' prescriptions at treatment initiation and their determinants, as well as biological therapy switches.

METHODS

Study design and study population

We analyzed administrative claims data from adult patients (≥18 years) enrolled in mandatory health insurance at Helsana Group, a leading health insurance provider in Switzerland, and who had at least one biological product claim between 2016 and 2021 (Table A1). The Helsana database covers 15% of the Swiss population (1.2 million Swiss residents). Previous studies have shown that this database can be considered fairly representative of the Swiss general population, as the results showed only minor discrepancies between raw and adjusted results [16, 17].

In Switzerland, medication reimbursement is governed by the Federal Law on Health Insurance, which mandates that basic health insurance must cover the costs of essential medications. Swissmedic regulates the market entry of medications, while the Federal Office of Public Health oversees the establishment of the reimbursement list, which determines the extent to which a medication is reimbursed. Switzerland's medication reimbursement system aims to balance access to essential medications with cost control: To be eligible for reimbursement, medications must demonstrate efficacy, safety, and cost-effectiveness compared to standard treatments. As such, all of the biological products included in this study are presumed to have fulfilled these requirements.

The study population for this research consisted of a total of 68'310 individuals who had at least one prescription of a biological or biosimilar medication between the years 2016 and 2021. Among this population, there were 53'379 individuals who had full mandatory health insurance coverage during the observation period. Furthermore, within this group, there were 17'654 individuals (or 18'953 IPs, respectively) who specifically received biological medications for which a biosimilar alternative was available at the time of dispensing.

Measures

The study included all patients who had at least one biosimilar available on the market at the time of IP of a biologic product. IP were defined for each patient as claims that were not preceded by other prescriptions in the same medication category within the previous 24 months. The following prescriptions were labeled as "follow-up prescriptions" (FP). We considered all claims of biological products within 12 months after IP. By restricting the follow-up period to 12 months, we were able to focus on the medications that were prescribed as a result of the initial prescription rather than medications that were prescribed for unrelated reasons. This approach allowed us to evaluate the impact of the initial prescription more accurately on subsequent medication use, and to draw meaningful conclusions about prescribing patterns over time. We selected 117 biological products approved by Swissmedic from a list (Table A1) derived from the Swiss Drug Compendium that details all unique reference products and the corresponding imitator medications (based on matching, unique combinations of active ingredient, dose, and package size). We considered patient characteristics as covariates. They included sex, age group (<50, 50-64, 65-74, >74) and language region (German, French, Italian). Furthermore, information on comorbidity was assessed using the number of Pharmaceutical Cost Groups (PCG) per patient (0,1,2,>2). This metric serves as a proxy for the presence of chronic disease [18]. The Swiss healthcare system offers different cost-sharing options to patients, including low (CHF 500, 1'000) or high deductibles (i.e., CHF 1'500, 2'000, or 2'500), and integrated care models, which aim to improve patient outcomes and reduce healthcare costs by coordinating care across different healthcare providers and settings. In Switzerland, patients who participate in integrated care models receive a premium rebate in exchange for limited healthcare provider options. Thus, having a low (CHF 500, 1'000) or high deductible (i.e., CHF 1'500, 2'000, or 2'500 vs. CHF 300), and being enrolled in a managed care model were used in the analysis. A comprehensive set of variables characterized the

prescribed medications: Prescriptions were described by category (fusion proteins, hormones, monoclonal antibodies, low-molecular-weight [LMW] heparins and growth factors), whether there were multiple packaging sizes, the cost per package of the reference product (in CHF, 100, 100-599, >600) and the relative price difference of the reference product to the corresponding biosimilar (10, 10-19, >20). We also assessed the number of available imitator drugs (1, 2, >2) on the market at the date of prescription. The analysis adds the aspect of healthcare provider by including information on the supply channel (general practitioner, outpatient hospital, specialist, traditional pharmacy).

Since biological products are the focus of our analysis and they include various subgroups, it seems appropriate to address the wording of these medications to ensure consistent terminology: Throughout the manuscript, we refer to the totality of all biologically manufactured drugs by using the term "biological products", while the originator drugs are referred to as "biologics" or as "reference products". "Biosimilars" are the imitator drugs of reference products.

Statistical analysis

All research participants' baseline characteristics are shown as counts and percentages, or as mean and standard deviation for continuous variables. We compared patient characteristics for all individuals with and without biosimilar IP. For bivariate comparisons between patients with and without biosimilar IP, Fisher exact and Chi-Square tests were used accordingly. Statistical significance was defined as a two-sided p-value of 0.05. We determined the biosimilar prevalence by distinguishing between IP and FP and the prevalence of biological therapy switches (number of prescriptions and patients) for each year (2016-2021). Chi-squared tests were used to determine whether the prevalence was equivalent across the years. To assess the determinants of biosimilar prescriptions, we used logistic regression models in which the

dependent variable was whether a biosimilar was prescribed as IP (0 or 1). Three different logistic models with different sets of variables were computed (Table A8). Both, Model B and C, show similar results and a better fit of the estimates compared to Model A based on the goodness-of-fit criteria (AIC, BIC). For the manuscript, we proceed with Model C because we are mainly interested in the associations with biosimilar prescriptions from all three points of view (patient, medication, physician). Odds ratios (OR) and corresponding 95% confidence intervals (CI) were calculated for each regression coefficient. The success rate in the binomial model was denoted by the term "occurrence" to improve the results' readability. All analyses were performed using R version 4.2.1.

RESULTS

The study sample consisted of 18'953 patients with at least one prescription of biological products. Patient characteristics of the study population at the time of IP, stratified by type of IP (reference product 81.5%, biosimilar 18.5%), are presented in Table 1. Female patients more frequently received biosimilars than males (60.6%). The mean age was slightly higher in men (61.7 years) compared to women (59.0 years). LMW heparins were the most prescribed reference products (54.2%), with growth hormones constituting the largest group of biosimilars (57.9%).

Table 1. Comparison of patient characteristics at IP between patients with reference product and biosimilar as IP.

Variables, n (%)	Total	Patients with IP = Reference product	Patients with IP = Biosimilar	p-value
Observations	18'953	15'453 (81.5%)	3'500 (18.5%)	
Female sex	11'678 (61.6%)	9'558 (61.9%)	2'120 (60.6%)	[1]
Age group				*** [2]
<50	5'501 (29.0%)	4'613 (29.9%)	888 (25.4%)	
50-64	4'720 (24.9%)	3'764 (24.4%)	956 (27.3%)	
65-74	3'963 (20.9%)	3'001 (19.4%)	962 (27.5%)	
>74	4'769 (25.2%)	4'075 (26.4%)	694 (19.8%)	
Language region				*** [2]

German	12'719 (67.1%)	9'958 (64.4%)	2'761 (78.9%)	
French	4'324 (22.8%)	3'777 (24.4%)	547 (15.6%)	
Italian	1'910 (10.1%)	1'718 (11.1%)	192 (5.5%)	
Number of comorbidities				** [2]
0	4'738 (25.0%)	3'901 (25.2%)	837 (23.9%)	
1	3'295 (17.4%)	2'664 (17.2%)	631 (18.0%)	
2	3'072 (16.2%)	2'448 (15.8%)	624 (17.8%)	
>2	7'848 (41.4%)	6'440 (41.7%)	1'408 (40.2%)	
Deductible				*** [2]
Low	15'765 (83.2%)	12'846 (83.1%)	2'919 (83.4%)	
Managed care	11'921 (62.9%)	9'790 (63.4%)	2'131 (60.9%)	** [1]
Category				*** [2]
Fusion proteins	360 (1.9%)	178 (1.2%)	182 (5.2%)	
Hormones	2'112 (11.1%)	1'697 (11.0%)	415 (11.9%)	
Monoclonal antibodies	2'908 (15.3%)	2'107 (13.6%)	801 (22.9%)	
LMW heparins	10'272 (54.2%)	10'196 (66.0%)	76 (2.2%)	
Growth factors	3'301 (17.4%)	1'275 (8.3%)	2'026 (57.9%)	
Multiple package size	16‘432 (86.7%)	13‘532 (87.6%)	2‘900 (82.9%)	*** [2]
Cost per package of reference product (in CHF)				*** [2]
<100	9'866 (52.1%)	9'652 (62.5%)	214 (6.1%)	
100-599	5'066 (26.7%)	3'179 (20.6%)	1'887 (53.9%)	
>600	4'021 (21.2%)	2'622 (17.0%)	1'399 (40.0%)	
Relative price difference (%)				*** [2]
<10	13'807 (72.8%)	11'546 (74.7%)	2'261 (64.6%)	
10-19	2'386 (12.6%)	1'871 (12.1%)	515 (14.7%)	
>20	2'760 (14.6%)	2'036 (13.2%)	724 (20.7%)	
Number of available imitator drugs				*** [2]
0	-	-	-	
1	12'490 (65.9%)	12'012 (77.7%)	478 (13.7%)	
2	2'741 (14.5%)	1'911 (12.4%)	830 (23.7%)	
>2	3'722 (19.6%)	1'530 (9.9%)	2'192 (62.6%)	
supply channel of first prescription				*** [2]
General practitioner	1'185 (6.3%)	1'097 (7.1%)	88 (2.5%)	
Outpatient hospital	6'224 (32.8%)	4'359 (28.2%)	1'865 (53.3%)	
Specialist	3'606 (19.0%)	2'674 (17.3%)	932 (26.6%)	
Traditional pharmacy	7'564 (39.9%)	6'981 (45.2%)	583 (16.7%)	
Rest	374 (2.0%)	342 (2.2%)	32 (0.9%)	

[1]) Fisher exact test, [2]) Chi-Square test
Signif. codes: '***' 0.001

The study found that a total of 17’654 patients were prescribed at least one biological product, with 56.9% of them (10’046 patients) receiving multiple prescriptions. Only 20.3% (3’600 patients) of those receiving biological products were prescribed at least one biosimilar during

the observation period. Among the patients who were prescribed biosimilars, 15.1% (2'672 patients) received multiple biosimilars.

Table 2 describes the overall frequency of biologicals products over the observation period including the absolute and relative frequency of biosimilars in comparison to all biological prescriptions. Of all biological products (IP and FP), 28.6% were biosimilar prescriptions. In absolute values, the prescription rate of biosimilars increased over time (from 1'016 in 2016 to 6'976 in 2021). However, there is no discernible trend in the relative share of biosimilars in all prescriptions of biological products (35.5% in 2016, 39.2% in 2017, 45.2% in 2018, 41.6% in 2019, 26.3% in 2020 and 22.5% in 2021). Furthermore, the share of biosimilars in FPs was higher than in IPs in every year. The growth factor Filgrastim was the most frequently prescribed active substance of biosimilars in IPs and FPs (53.1% and 36.2% respectively), while enoxaparin was the most frequently prescribed active substance of reference products in IPs and FPs (65.3% and 25.5%, respectively) (Table A2-A6).

Table 2. All prescriptions for which a biosimilar was approved at the time of the prescription

	total	2016	2017	2018	2019	2020	2021	
n	18'953	815	888	1'037	1'520	5'313	9'380	
Biosimilars (n, % of N)	3'500 (18.5%)	262 (32.1%)	343 (38.6%)	391 (37.7%)	612 (40.3%)	813 (15.3%)	1'079 (11.5%)	*** [1]
n	50'251	2'047	2'716	3'314	6'306	14'288	21'580	
Biosimilar (n, % of N)	16'293 (32.4%)	754 (36.8%)	1'071 (39.4%)	1'578 (47.6%)	2'644 (41.9%)	4'349 (30.4%)	5'897 (27.3%)	*** [1]

[1] Chi-Square test, Signif. codes: '***' <0.001

Of the study population, only a small subset (n=1'492, 8.5%) experienced at least one medication switch (Table 3). Most patients had switches between reference products (n=867, 58.1%), followed by switches from reference product to biosimilar (n=331, 22.2%), from biosimilar to reference product (n=297, 19.9%) and switches between biosimilars (n=286,

19.2%). The number of patients with at least one switch increased between 2016 and 2021 (from 28 to 662), whereby the numbers of patients with switches between reference products increased most prominently (from 25.0% in 2016 to 62.1% in 2021). Switches between reference products and between biosimilars occurred most often for Enoxaparin and Rituximab, respectively (Table A7). The most common switches from reference product to biosimilar and from biosimilar to reference products were most often observed for Filgrastim and Enoxaparin.

Table 3. Patients with biologic therapy switches

Switches, N=patients	Total	2016	2017	2018	2019	2020	2021	p-value
At least one, n	1'492	28	42	77	249	434	662	
Reference Prod to Reference Prod, n (%)	867 (58.1%)	7 (25.0%)	15 (35.7%)	37 (48.1%)	146 (58.6%)	251 (57.8%)	411 (62.1%)	***[1]
Biosimilar to Biosimilar, n (%)	286 (19.2%)	9 (32.1%)	10 (23.8%)	14 (18.2%)	51 (20.5%)	74 (17.1%)	128 (19.3%)	[1]
Reference Prod to Biosimilar, n (%)	331 (22.2%)	6 (21.4%)	11 (26.2%)	21 (27.3%)	60 (24.1%)	103 (23.7%)	130 (19.6%)	[1]
Biosimilar to Reference Prod, n (%)	297 (19.9%)	10 (35.7%)	8 (19.0%)	15 (19.5%)	49 (19.7%)	96 (22.1%)	119 (18.0%)	[1]

[1]) Chi-Square test
Signif. codes: '***' <0.001

As far as the regression results are concerned, the odds of prescribing biosimilars at IP have been increasing over the years (Fig.1, Table A8). Male sex was associated with 13.2% higher odds of receiving biosimilar IP, whereas residence in a French or Italian-speaking region had a 38.9% and 23.9%, respectively, lower occurrence of a biosimilar IP. None of the insurance-related variables showed a significant association with biosimilars IPs. In terms of pharmaceutical variables, monoclonal antibodies, LMW heparins and growth factors were associated with substantially lower biosimilar IP occurrences (-88.5%, -99.9% and -84.2%) than fusion proteins. The availability of multiple packaging sizes was associated with 4.6-fold higher odds of biosimilar IP compared to medications with solely one packaging size. For the absolute package price, no consistent pattern was observed, as medications with prices between

100 and 599 francs per pack decreased the odds by 79.8% compared to the baseline (<100 CHF), whereas the odds in the highest prize category (>600 CHF) were lower by 34.3%. However, compared to products with a <10% price difference between reference product and biosimilar, higher price reductions were associated with decreased occurrence of biosimilar IP: medications with 10-19% price difference had 92.4% lower odds and medications with more than 20% had even 93.3% lower odds. On the contrary, increasing the number of available imitator medications of prescription (2 and >2) had substantially higher (2.36-fold and 9.65-fold) odds of biosimilar IP compared to prescriptions with only one available biosimilar. As far as provider variables are concerned, physicians in the outpatient hospital setting prescribed far more biosimilars compared to general practitioners (2.48-fold higher odds). The occurrence of biosimilar IP was also 41.7% higher in patients who had been prescribed biological products by a specialist than in patients who had received the equivalent medications from a general practitioner.

DISCUSSION

The growing market for biosimilars can explain the observed increase in the number of biosimilar prescriptions over time: from 15 approved biosimilars in 2016 the market for biosimilars has grown (15 in 2017; 22 in 2018; 42 in 2019; 70 in 2020) up to 78 biosimilars in 2021 (Table A1) [7, 19]. A longer time on the market gives the biosimilar a better chance to establish itself and gain market share. Despite the increase, the biosimilars quota remained relatively low. In the literature, this low share in Switzerland has already been documented: in 2019, market sales of all biological products with available biosimilars totaled CHF 449 million in 2019, of which biosimilars accounted for only CHF 42 million (9.4%) [7]. Furthermore, market share of biosimilars seems to be low compared to other countries. For example, biosimilars account for 80% of the biological product market in Norway [20]. In Germany, two

studies reported an average biosimilar ratio between 40.5% and 51.9% in 2019 [21, 22]. In the present study we observed substantially lower average biosimilar quota of 28.0%. Infliximab is a particularly compelling example, with the biosimilar share reaching 26% in Germany after only 12 months on the market (2017) and rising to 64-68% of the biosimilar market in 2019. By contrast, infliximab achieved a market share of only 22% in Switzerland in 2019 [7]. The low market share of biosimilars in Switzerland may be due to various reasons: Studies have shown that knowledge deficits among physicians and among patients may lead to reluctance regarding the use of biosimilars [11–14]. According to survey studies [23–27], between 15-30% of the population is thought to have a negative perception of these imitator drugs. This distrust may be driven by a perceived weakness in the evidence base concerning efficacy and safety of biosimilars, as only bioequivalence needs to be demonstrated for biosimilar approval. However, there is increasing evidence of equivalent safety and efficacy of biosimilars, along with evidence of bioequivalence [28–30]. Furthermore, a challenge for newly approved biosimilars is the difficulty in extending conclusions from RCTs to the broader population that will use the biosimilar. This is because RCTs typically enroll a more homogeneous population, and certain patient groups, such as pediatric, elderly, and comorbid populations, as well as patients with polypharmacy, are often underrepresented in these trials [31–33]. As a result, prescribers may be skeptical about the use of biosimilars in these patient populations because of the lack of data. Moreover, the current incentive system discourages the prescription of biosimilars for self-dispensing doctors and pharmacies as they are rewarded for prescribing the more expensive product by a bigger profit margin [7]. On the other side, under a capitation payment model, managed care physicians may have a financial incentive to prescribe lower-cost biosimilars in order to maximize profits. However, if physicians are not properly educated about the safety and efficacy of biosimilars, they may be hesitant to prescribe them.

That only a small subset (n=1'492, 8.5%) experienced at least one medication switch can be explained by the reluctance of patients to switch to a biosimilar medication due to the fear of experiencing new and unknown side effects. Patients who have been using a particular medication for a long time and have become accustomed to its efficacy and safety profile may be hesitant to switch to a biosimilar, which they perceive as being different and possibly inferior. Nevertheless, efficacy of biosimilar switching has been observed [7, 28–30, 34, 35]. According to a systematic literature review based on 90 published studies, the great majority of the publications did not report differences in immunogenicity, safety, or efficacy when patients switched to biosimilars. Three large studies did not show differences in efficacy or safety after multiple switches between reference product and biosimilar [36–38]. Only two publications reported a loss of efficacy or increased dropout rates [39, 40]. Often, this very knowledge and awareness about the safety and efficacy of switching to new treatment options lack for prescribing physicians who rely on solid, evidence-based data to make treatment decisions [41–43].

The regression results revealed that biosimilar IP rates were lower in French-speaking cantons. These regional variations may be caused by a variety of variables, including a higher concentration of medical services in urban regions, various patient characteristics, and cultural variations between cantons [44, 45]. The strongest barrier for biosimilar prescriptions was the increasing relative price difference between biosimilar and reference product. A possible explanation is that healthcare providers may have less experience with biosimilars with a higher price difference or may perceive them as less established and less proven than biosimilars with a lower price difference. This lack of familiarity or perceived risk may contribute to reluctance in prescribing biosimilars with a higher price difference. It is also important to consider the role of financial incentives and reimbursement policies in biosimilar prescribing: Currently, dispensation channels receive a larger profit margin when distributing the more expensive

reference product under the present price-dependent margin [19]. This incentive system seems to be characteristic for Switzerland, as studies conducted in European countries did not find a relationship between price difference and biosimilar dissemination [46–48]. This might be attributed to several factors that differentiate Switzerland from other European countries: Cantonal differences in self-dispensing regulation, the country's different prescribing cultures and guidelines across its language regions, and capitation is implemented only in relatively few cases in Switzerland. In our analysis, male patients had more biosimilar IP. According to studies, women were often more skeptical of imitator drugs [23, 49–52] and they more frequently believe that they are more responsive to medications than men [53–55]. This can have an impact on their confidence in biosimilars, making female patients more aware of potential side effects or lack thereof. Biosimilar IPs were prescribed more frequently for fusion proteins compared to other categories which indicates an increased acceptance of imitator products in this drug class. This is supported by the relatively early market entry (2018) and by a meta-analysis showing comparable results in terms of efficacy and safety between reference product and biosimilars [56]. The strongest facilitator of biosimilar prescriptions was the amount of available biosimilars, which is in line with the findings of a prior study [46, 57]. Thus, the replacement of reference products by biosimilars seems to be better accepted in market segments with many imitator products. This finding is probably associated with the larger collective promotional effort from multiple players involved in the field to favor biosimilars; it is noteworthy that the largest adoption of biosimilars (Filgrastim) has been partially attributable to the fact that numerous biosimilar producers have commercialized different products, whereas there is only one company branding the reference product [58]. We found more biosimilar IPs for specialists and outpatient hospital physicians than GP. These findings are in line with existing literature that showed more biosimilars from specialists who reported a higher confidence in the comparability of biosimilars than GPs [59, 60]. Differences

in care providers may be due to a variety of reasons: some healthcare providers may not be interested in stockpiling too many different medications and additional biosimilars, as they sometimes have large storage requirements (cooling, expiration date) and , thus, are associated with a significant financial risk [19]. In addition, it has been demonstrated that the dissemination of knowledge about new prescription options is heterogeneous because there are large learning costs associated with the treatment effects of new therapy options, which rely on the training and experience of the doctor [61]. Despite the fact that a previous study conducted in the context of generic drugs showed that older people are less likely to use imitator products when offered a choice [23, 57], we did not observe an age-dependency of biosimilar prescriptions.

The most valuable strength of this study is the extensive dataset of biosimilar prescriptions and potential influencing factors including sociodemographic, pharmaceutical and healthcare provider variables that were gathered from a representative sample of the Swiss population. The main limitation is the dearth of clinical data in our database (e.g., disease severity, clinical diagnosis, and reason for biosimilar utilization). However, we attempted to mitigate this by utilizing comorbidity measures based on reimbursed prescriptions to control for potential confounders. Another limitation of our study is that the follow-up period for the prescriptions was limited to 12 months. This time frame may have led to the exclusion of some prescriptions, potentially introducing bias into our results. Nevertheless, we observed that a significant number of patients (7'608, which accounts for 43.1% of the total) were given only one prescription, indicating that any bias arising from this limitation is expected to be insignificant. The relatively low market share of biosimilars compared to other EU countries highlighted in our research paper has important implications for the adoption and utilization of these products in Switzerland. Patients and physicians should be better and objectively informed about biosimilars in order to increase the acceptance [47, 48]. Also, for example, a clear and conspicuous indication of the prescribed active substance on the medication package for both

the reference product and the imitator drug, for instance, could enhance patient confidence [42]. To address the perceived uncertainty and mistrust in imitator products, the evidence base should be further strengthened: direct evidence to help explain some of the practical aspects related to the use of biosimilars can be provided by retrospective studies, national databases and registries that track the long-term immunogenicity and safety of biosimilars [62–67]. In addition, the incentive system for healthcare providers seems to be designed in such a way that fewer biosimilars are prescribed. Thus, these incentives should be eliminated, for example by introducing a fixed margin that always remunerates the medication supplier the same regardless of the prescribed product (reference product or biosimilar). In order to exploit the cost saving potential of biosimilars, the aforementioned measures should be targeted to biosimilars with a noticeable price difference compared to their reference products, and that still possess relatively low biosimilar market share. Taking into account the findings presented in Table A6, notable examples of these biosimilars include Bevacizumab, Follitropin alfa, and Pegfilgrastim.

However, the decision to prescribe an imitator drug should not merely be motivated by the cost-saving potential but should ensure appropriate health care provision for the patients. Therefore, it is crucial for healthcare providers to engage in shared-decision making with their patients to determine the most appropriate treatment option based on their individual medical situation.

CONCLUSION

Despite an increase of available biosimilars in Switzerland between 2016 and 2021, the biosimilars market share remained relatively low over time. In addition, biological therapy switches were rarely observed, highlighting the importance of IPs. Our study suggests that greater acceptance and higher utilization of biosimilars may be associated with the availability

of different package sizes and lower price differences between biosimilars and their reference products. Patients and providers should be informed about biosimilars in a timely and appropriate manner, and outdated incentive structures have to be changed to increase the use of biosimilars.

[please insert Appendix here]

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Author contributions KW, MN and CH designed the study. MN did data preparation and data management. MN and KW performed the statistical analyses, with the contribution of SB, CH and EB. KW drafted the main manuscript text. All authors assisted in the interpretation of the results and critically revised the manuscript. All authors have read and approved the manuscript.

Data availability Helsana provides the data that support up the findings of this research. (https://www.helsana.ch/en/helsana-group). These data, which were used under license for the present study and are not accessible to the general public, are subject to restrictions. But with Helsana's consent and upon reasonable request, data are available from the authors (gesundheitskompetenz@helsana.ch).

Ethics approval The data used in this study were retrospective, pre-existing, de-identified, and anonymous in accordance with privacy laws and regulations. This study was free from the provisions of the Swiss Federal Law on Human Research because it used retrospective, de-identified, and anonymized data (Humanforschungsgesetz) [68] and was thus exempted from receiving clearance from the regional ethics committee (the ethical committee of the Canton of Zurich) as well as from obtaining the patients' informed consent.

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Consent to publish Not applicable.

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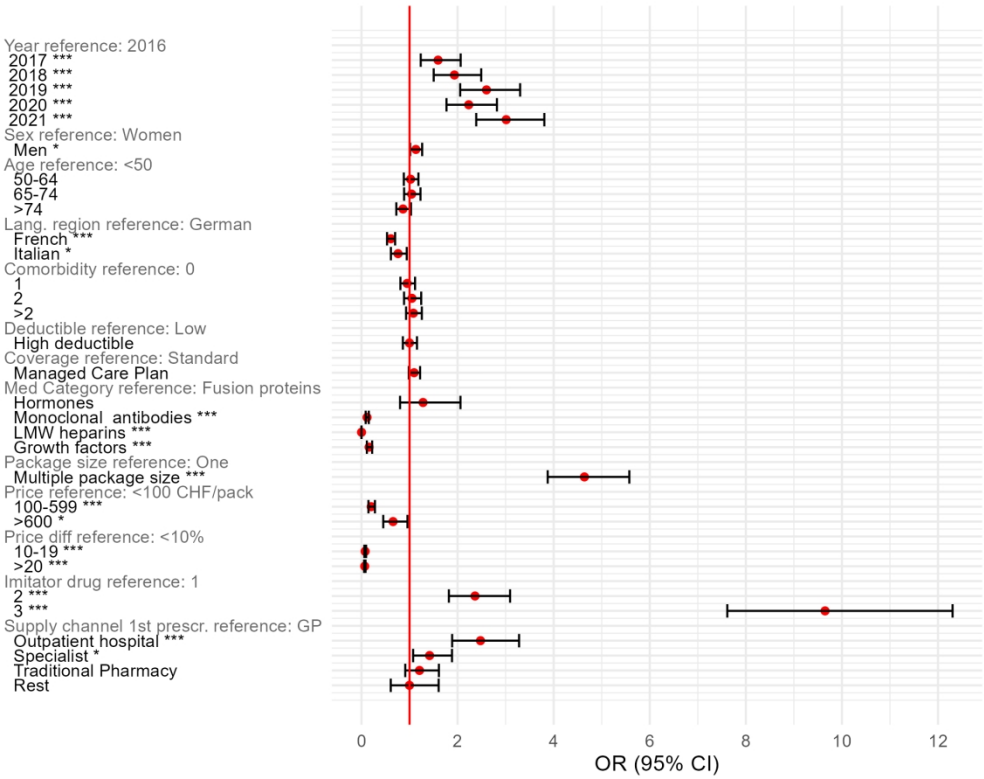
Figure title legend

598 **Figure 1 Determinants of biosimilar initial prescription (logistic regression)**



177x140mm (300 x 300 DPI)

Table A1 Substitution catalogue: reference product & biosimilar (2016-2021)

ATC	Reference Product			Biosimilar			
	medication	Dose (mg) / unit	cost (in CHF)	medication	Reimburment date	Dose (mg) / unit	cost (in CHF)
Low-molecular-weight heparins							
B01	Clexane	20 / 10	41	Inhixa	01.08.2020	20 / 10	38.55
B01	Clexane	20 / 50	139.55	Inhixa	01.08.2020	20 / 50	127.25
B01	Clexane	40 / 2	17.35	Inhixa	01.08.2020	40 / 2	16.45
B01	Clexane	40 / 10	62.45	Inhixa	01.08.2020	40 / 10	57.85
B01	Clexane	40 / 50	246.75	Inhixa	01.08.2020	40 / 50	223.7
B01	Clexane	60 / 10	76.65	Inhixa	01.08.2020	60 / 10	70.6
B01	Clexane	80 / 10	102.3	Inhixa	01.08.2020	80 / 10	93.7
B01	Clexane	100 / 10	123.75	Inhixa	01.08.2020	100 / 10	113
B01	Clexane	120 / 10	134.9	Inhixa	01.08.2020	120 / 10	123.05
B01	Clexane	150 / 10	161.3	Inhixa	01.08.2020	150 / 10	146.8
B01	Clexane	300 / 1	41.3	Inhixa	01.08.2020	300 / 1	38.8
Growth factors							
L03	Neupogen	0.3 / 5	531.1	Accofil	01.11.2019	0.3 / 5	479.65
				Filgrastim-Teva	01.03.2010	0.3 / 5	479.65
				Zarzio	01.05.2010	0.3 / 5	479.65
L03	Neupogen	0.48 / 5	740.9	Accofil	01.11.2019	0.48 / 5	668.45
				Filgrastim-Teva	01.03.2010	0.48 / 5	668.45
				Zarzio	01.05.2010	0.48 / 5	668.45
L03	Neulasta	6 / 1	1668.75	Grasustek	01.09.2021	6 / 1	1266.95
				Pelgraz	01.11.2019	6 / 1	1266.85
				Pelgraz	01.11.2019	6 / 1	1266.85
				Pelmeg	01.01.2020	6 / 1	857.55
				Ziextenzo	01.03.2020	6 / 1	1266.95
				Fulphila	01.06.2020	6 / 1	1266.85
B03	Eprex	0.008 / 6	71.5	Binocrit	01.10.2009	0.008 / 6	66.15
B03	Eprex	0.017 / 6	126.55	Binocrit	01.10.2009	0.017 / 6	115.7
B03	Eprex	0.025 / 6	181.65	Binocrit	01.10.2009	0.025 / 6	165.25
B03	Eprex	0.037 / 6	236.75	Binocrit	01.10.2009	0.037 / 6	214.7
B03	Eprex	0.046 / 6	291.8	Binocrit	01.10.2009	0.046 / 6	264.5
B03	Eprex	0.092 / 6	567.2	Binocrit	01.10.2009	0.092 / 6	512.1
Hormones							
A10	Lantus	10.9 / 5	81.85	Abasaglar	01.09.2015	10.9 / 5	68.4
G03	GONAL-F	0.022 / 1	156.4	Ovaleap	01.11.2018	0.022 / 1	122.05
G03	GONAL-F	0.033 / 1	226.45	Ovaleap	01.11.2018	0.033 / 1	174.95

G03	GONAL-F	0.066 / 1	430.65	Ovaleap	01.11.2018	0.066 / 1	329.1
H01	Genotropin	5 / 1	221.65	Omnitrope	01.11.2010	5 / 1	201.1
H01	Genotropin	5 / 5	1041.9	Omnitrope	01.11.2010	5 / 5	940
H05	Forsteo	0.25 / 1	412.75	Movymia	01.09.2019	0.25 / 1	340.75
				Terrosa	01.09.2019	0.25 / 1	340.75
				Terrosa	01.09.2019	0.25 / 1	340.75
Fusion proteins							
L01	MabThera	100 / 2	627.3	Rixathon	01.09.2018	100 / 2	505.5
				Truxima	01.01.2019	100 / 2	505.5
L01	MabThera	500 / 1	1515.65	Rixathon	01.09.2018	500 / 1	1225.7
				Truxima	01.01.2019	500 / 1	1225.7
L01	Herceptin	150 / 1	686.4	Herzuma	01.12.2021	150 / 1	562.45
				Trazimera	01.10.2019	150 / 1	562.45
				Kanjinti	01.02.2020	150 / 1	562.45
				Ogivri	01.09.2020	150 / 1	562.45
L01	Herceptin	440 / 1	1932.85	Herzuma	01.12.2021	150 / 1	1586.75
				Trazimera	01.10.2019	150 / 1	1586.75
				Kanjinti	01.02.2020	150 / 1	1586.75
				Ogivri	01.09.2020	150 / 1	1586.75
L01	Avastin	100 / 1	410.65	Oyavas	01.08.2021	100 / 1	312.1
				Bevacizumab-Teva	01.07.2021	100 / 1	312.1
				MVASI	01.07.2020	100 / 1	312.1
				Zirabev	01.08.2020	100 / 1	312.1
L01	Avastin	400 / 1	1469.5	Oyavas	01.08.2021	400 / 1	1117.5
				Bevacizumab-Teva	01.07.2021	400 / 1	1117.5
				MVASI	01.07.2020	400 / 1	1117.5
				Zirabev	01.08.2020	400 / 1	1117.5
L04	Enbrel	25 / 4	682.35	Benepali	01.04.2019	25 / 4	515.8
				Erelzi	01.07.2018	25 / 4	515.8
L04	Enbrel	50 / 2	669.05	Benepali	01.04.2019	50 / 2	504.3
				Erelzi	01.07.2018	50 / 2	505.9
L04	Remicade	100 / 1	695.75	Inflectra	01.08.2016	100 / 1	627.25
				Remsima	01.01.2016	100 / 1	627.25
L04	Humira	20 / 2	661.8	Hyrimoz	01.11.2019	20 / 2	500.45
L04	Humira	40 / 1	661.8	Abrilada	01.06.2021	40 / 1	500.45
				Amgevita	01.11.2019	40 / 1	500.45
				Hyrimoz	01.11.2019	40 / 1	500.45
				Idacio	01.08.2020	40 / 1	500.45
				Imraldi	01.07.2020	40 / 1	498.55
				Hulio	01.08.2020	40 / 1	500.45

Table A2 First Prescriptions: Reference Products (active substance)

Active substance	total	2016	2017	2018	2019	2020	2021
n	14'987	433 (2.9%)	394 (2.6%)	501 (3.3%)	861 (5.7%)	4'525 (30.2%)	8'273 (55.2%)
Adalimumab	369 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	24 (2.8%)	182 (4.0%)	163 (2.0%)
Bevacizumab	267 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	96 (2.1%)	171 (2.1%)
Enoxaparin	9'785 (65.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3'047 (67.3%)	6'738 (81.4%)
Epoetin alfa	136 (0.9%)	20 (4.6%)	30 (7.6%)	19 (3.8%)	23 (2.7%)	24 (0.5%)	20 (0.2%)
Etanercept	176 (1.2%)	0 (0.0%)	0 (0.0%)	37 (7.4%)	55 (6.4%)	38 (0.8%)	46 (0.6%)
Filgrastim	658 (4.4%)	158 (36.5%)	134 (34.0%)	107 (21.4%)	85 (9.9%)	104 (2.3%)	70 (0.8%)
Follitropin alfa	747 (5.0%)	0 (0.0%)	0 (0.0%)	41 (8.2%)	182 (21.1%)	226 (5.0%)	298 (3.6%)
Infliximab	530 (3.5%)	141 (32.6%)	103 (26.1%)	74 (14.8%)	68 (7.9%)	68 (1.5%)	76 (0.9%)
Insulin glargin	640 (4.3%)	113 (26.1%)	127 (32.2%)	126 (25.1%)	102 (11.8%)	88 (1.9%)	84 (1.0%)
Pegfilgrastim	457 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	35 (4.1%)	225 (5.0%)	197 (2.4%)
Rituximab	661 (4.4%)	0 (0.0%)	0 (0.0%)	97 (19.4%)	203 (23.6%)	178 (3.9%)	183 (2.2%)
Somatropin	5 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	2 (0.0%)	0 (0.0%)
Teriparatid	304 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	55 (6.4%)	134 (3.0%)	115 (1.4%)
Trastuzumab	252 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	27 (3.1%)	113 (2.5%)	112 (1.4%)

Table A3 First Prescriptions: Biosimilars (active substance)

Active substance	total	2016	2017	2018	2019	2020	2021
n	3'489	261 (7.5%)	344 (9.9%)	393 (11.3%)	616 (17.7%)	809 (23.2%)	1'066 (30.6%)
Adalimumab	165 (4.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (1.1%)	63 (7.8%)	95 (8.9%)
Bevacizumab	28 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (0.6%)	23 (2.2%)
Enoxaparin	76 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (0.9%)	69 (6.5%)
Epoetin alfa	34 (1.0%)	8 (3.1%)	2 (0.6%)	7 (1.8%)	9 (1.5%)	3 (0.4%)	5 (0.5%)
Etanercept	185 (5.3%)	0 (0.0%)	0 (0.0%)	10 (2.5%)	49 (8.0%)	69 (8.5%)	57 (5.3%)
Filgrastim	1'854 (53.1%)	243 (93.1%)	271 (78.8%)	295 (75.1%)	342 (55.5%)	336 (41.5%)	367 (34.4%)
Follitropin alfa	219 (6.3%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	40 (6.5%)	71 (8.8%)	107 (10.0%)
Infliximab	281 (8.1%)	7 (2.7%)	31 (9.0%)	49 (12.5%)	54 (8.8%)	61 (7.5%)	79 (7.4%)
Insulin glargin	141 (4.0%)	0 (0.0%)	39 (11.3%)	29 (7.4%)	33 (5.4%)	21 (2.6%)	19 (1.8%)
Pegfilgrastim	129 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	32 (4.0%)	97 (9.1%)
Rituximab	318 (9.1%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	78 (12.7%)	120 (14.8%)	119 (11.2%)
Somatropin	5 (0.1%)	3 (1.1%)	1 (0.3%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Teriparatid	47 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.6%)	20 (2.5%)	23 (2.2%)
Trastuzumab	7 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	6 (0.6%)

Table A4 Rest prescriptions: Reference Products (active substance)

Active substance	total	2016	2017	2018	2019	2020	2021
n	33'958	1'293 (3.8%)	1'645 (4.8%)	1'736 (5.1%)	3'662 (10.8%)	9'939 (29.3%)	15'683 (46.2%)
Adalimumab	3'070 (9.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	41 (1.1%)	1'354 (13.6%)	1'675 (10.7%)
Bevacizumab	2'109 (6.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	481 (4.8%)	1'628 (10.4%)
Enoxaparin	8'669 (25.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2'343 (23.6%)	6'326 (40.3%)
Epoetin alfa	2'052 (6.0%)	234 (18.1%)	385 (23.4%)	408 (23.5%)	200 (5.5%)	422 (4.2%)	403 (2.6%)
Etanercept	791 (2.3%)	0 (0.0%)	0 (0.0%)	90 (5.2%)	310 (8.5%)	198 (2.0%)	193 (1.2%)
Filgrastim	2'252 (6.6%)	408 (31.6%)	428 (26.0%)	403 (23.2%)	275 (7.5%)	403 (4.1%)	335 (2.1%)
Follitropin alfa	1'914 (5.6%)	0 (0.0%)	0 (0.0%)	19 (1.1%)	502 (13.7%)	561 (5.6%)	832 (5.3%)
Infliximab	2'973 (8.8%)	543 (42.0%)	660 (40.1%)	424 (24.4%)	434 (11.9%)	435 (4.4%)	477 (3.0%)
Insulin glargin	1'036 (3.1%)	108 (8.4%)	170 (10.3%)	134 (7.7%)	443 (12.1%)	112 (1.1%)	69 (0.4%)
Pegfilgrastim	1'426 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	78 (2.1%)	699 (7.0%)	649 (4.1%)
Rituximab	3'148 (9.3%)	0 (0.0%)	0 (0.0%)	258 (14.9%)	1'177 (32.1%)	814 (8.2%)	899 (5.7%)
Somatropin	7 (0.0%)	0 (0.0%)	2 (0.1%)	0 (0.0%)	2 (0.1%)	3 (0.0%)	0 (0.0%)
Teriparatid	1'791 (5.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	79 (2.2%)	856 (8.6%)	856 (5.5%)
Trastuzumab	2'720 (8.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	121 (3.3%)	1'258 (12.7%)	1'341 (8.6%)

Table A5 Rest prescriptions: Biosimilars (active substance)

Active substance	total	2016	2017	2018	2019	2020	2021
n	16'293	754 (4.6%)	1'071 (6.6%)	1'578 (9.7%)	2'644 (16.2%)	4'349 (26.7%)	5'897 (36.2%)
Adalimumab	3'100 (19.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	64 (2.4%)	1'256 (28.9%)	1'780 (30.2%)
Bevacizumab	306 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	21 (0.5%)	285 (4.8%)
Enoxaparin	41 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.1%)	38 (0.6%)
Epoetin alfa	844 (5.2%)	32 (4.2%)	114 (10.6%)	257 (16.3%)	369 (14.0%)	55 (1.3%)	17 (0.3%)
Etanercept	930 (5.7%)	0 (0.0%)	0 (0.0%)	23 (1.5%)	247 (9.3%)	377 (8.7%)	283 (4.8%)
Filgrastim	5'894 (36.2%)	695 (92.2%)	752 (70.2%)	897 (56.8%)	1'110 (42.0%)	1'142 (26.3%)	1'298 (22.0%)
Follitropin alfa	583 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	74 (2.8%)	210 (4.8%)	299 (5.1%)
Infliximab	1'507 (9.2%)	23 (3.1%)	115 (10.7%)	274 (17.4%)	278 (10.5%)	374 (8.6%)	443 (7.5%)
Insulin glargin	509 (3.1%)	0 (0.0%)	80 (7.5%)	126 (8.0%)	143 (5.4%)	98 (2.3%)	62 (1.1%)
Pegfilgrastim	406 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	125 (2.9%)	281 (4.8%)
Rituximab	1'763 (10.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	356 (13.5%)	564 (13.0%)	843 (14.3%)
Somatropin	16 (0.1%)	4 (0.5%)	10 (0.9%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
Teriparatid	297 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	114 (2.6%)	181 (3.1%)
Trastuzumab	97 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (0.2%)	87 (1.5%)

Table A6 Biosimilars quota by active substance

Active substance	Avg. relative Price difference	Biosimilars quota (IP+RP) 2016	2017	2018	2019	2020	2021
Adalimumab	24.63	-	-	-	52.21	46.2	50.5
Bevacizumab	23.98	-	-	-	-	4.31	14.62
Enoxaparin	7.77	-	-	-	-	<1	<1
Epoetin alfa	8.91	3.1	21.85	38.21	62.9	11.51	4.94
Etanercept	24.52	-	-	20.63	44.78	65.4	58.72

Filgrastim	9.73	62.37	64.54	70.04	80.13	74.46	80.43
Follitropin alfa	22.76	-	-	1.64	14.29	26.31	26.43
Infliximab	9.85	4.2	15.53	39.34	39.81	46.38	48.56
Insulin glargin	16.43	-	33.62	37.35	24.41	37.3	34.62
Pegfilgrastim	48.61	-	-	-	-	14.52	30.88
Rituximab	19.27	-	-	<1	23.93	40.81	47.06
Somatropin	9.53	87.5	84.62	100	20	0	-
Teriparatid	17.44	-	-	-	4.29	11.84	17.36
Trastuzumab	17.98	-	-	-	-	<1	6.02

Table A7 Frequency of medication switches by active substance

Category	Active substance	Proportion to all switches (%)			
		RP to RP	RP to B	B to B	B to RP
Fusion proteins	Etanercept	0.27	4.4	0.29	1.59
Hormones	Follitropin alfa	9.41	5.35	8.1	5.84
Hormones	Insulin glargin	0.27	2.95	0.17	2.72
Hormones	Somatropin	0.02	0.07	0	0
Hormones	Teriparatid	0.21	1.42	1.34	2.51
Monoclonal antibodies	Adalimumab	4.52	4.04	1.75	4.63
Monoclonal antibodies	Bevacizumab	11.38	1.67	4.31	5.98
Monoclonal antibodies	Infliximab	1.86	8.95	2.33	6.4
Monoclonal antibodies	Rituximab	21.81	11.75	31.24	13.05
Monoclonal antibodies	Trastuzumab	6.94	1.02	1.52	7.89
Low-molecular-weight heparins	Enoxaparin	25.57	0.65	0.06	30.88
Growth factors	Epoetin alfa	14.22	1.16	24.94	1.17
Growth factors	Filgrastim	2.4	50.75	21.5	8.07
Growth factors	Pegfilgrastim	1.13	5.82	2.45	9.27

Table A8 Three models (A-C) assessing determinants of biosimilar first prescription (logistic regression)

Variables	**Model A: sociodemographic variables** Coeff. [95%CI]	**Model B: Model A + medication variables** Coeff. [95%CI]	**Model C: Model B + provider variables** Coeff. [95%CI]
Intercept	0.429 [0.355, 0.518]	0.831 [0.49, 1.402]	0.706 [0.399, 1.241]
Year:			
2016 (reference)			
2017	1.381 [1.129, 1.692]	1.602 [1.246, 2.062]	1.594 [1.233, 2.064]
2018	1.354 [1.113, 1.648]	1.983 [1.551, 2.539]	1.934 [1.503, 2.492]
2019	1.493 [1.246, 1.793]	2.64 [2.094, 3.332]	2.602 [2.054, 3.302]
2020	0.42 [0.356, 0.497]	2.203 [1.755, 2.769]	2.232 [1.769, 2.819]
2021	0.302 [0.256, 0.355]	3.077 [2.452, 3.867]	3.012 [2.388, 3.806]
Sex:			
Female (reference)			
Male	0.998 [0.922, 1.081]	1.137 [1.02, 1.267]	1.132 [1.014, 1.263]

Age:			
<50 (reference)			
50-64	1.302 [1.169, 1.452]	1.005 [0.867, 1.164]	1.022 [0.881, 1.185]
65-74	1.571 [1.401, 1.761]	1.044 [0.889, 1.227]	1.044 [0.887, 1.228]
>74	0.961 [0.849, 1.086]	0.825 [0.694, 0.98]	0.864 [0.725, 1.03]
Language region			
German (reference)			
French	0.578 [0.521, 0.64]	0.582 [0.51, 0.664]	0.611 [0.532, 0.7]
Italian	0.467 [0.397, 0.546]	0.744 [0.601. 0.918]	0.761 [0.612, 0.942]
Number of comorbidity:			
0 (reference)			
1	1.054 [0.932, 1.191]	0.934 [0.796, 1.094]	0.95 [0.81, 1.115]
2	1.095 [0.963, 1.244]	1.041 [0.88, 1.23]	1.05 [0.886, 1.243]
>2	0.938 [0.837, 1.051]	1.05 [0.904, 1.22]	1.08 [0.928, 1.256]
Deductible:			
Low (reference)			
High	1.067 [0.954, 1.192]	1.005 [0.868, 1.163]	0.998 [0.861, 1.155]
Managed care	1.029 [0.949, 1.116]	1.103 [0.992, 1.226]	1.095 [0.984, 1.22]
Category:			
Fusion proteins (reference)			
Hormones		1.297 [0.816, 2.081]	1.281 [0.803, 2.06]
Monoclonal antibodies		0.152 [0.116, 0.199]	0.115 [0.087, 0.152]
Low-molecular-weight heparins		0.001 [0.001, 0.001]	0.001 [0, 0.001]
Growth factors		0.235 [0.168, 0.327]	0.158 [0.112, 0.222]
Multiple package size		4.551 [3.808, 5.461]	4.64 [3.876, 5.575]
Cost per package of reference product (in CHF)			
<100			
100-599		0.254 [0.185, 0.349]	0.202 [0.145, 0.28]
>600		0.853 [0.592, 1.236]	0.657 [0.453, 0.957]
Relative price difference (%)			
<10			
10-19		0.091 [0.072, 0.115]	0.076 [0.059, 0.096]
>20		0.067 [0.053, 0.084]	0.067 [0.054, 0.084]
Number of available imitator drug:			
1 (reference)			
2		2.15 [1.671, 2.785]	2.363 [1.819, 3.093]
>2		8.143 [6.502, 10.248]	9.649 [7.614, 12.303]
Suppl			
General practicioner (reference)			
Outpatient hospital			2.477 [1.887, 3.28]
Specialist			1.417 [1.075, 1.884]
Traditional pharmacy			1.207 [0.911, 1.611]
Rest			0.998 [0.609, 1.606]
Observations	18'953	18'953	18'953
AIC	16'588	9'868	9'735
BIC	16'722	10'088	9'986

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	Title page
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	2,3

Objectives	#3	State specific objectives, including any prespecified hypotheses		3
Methods				
Study design	#4	Present key elements of study design early in the paper		3,4,5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		4,5,6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.		4
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	n/a. The resent study does not contain matched studies	
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable		4,5,6
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.		3,4

Bias	#9	Describe any efforts to address potential sources of bias	6,7
Study size	#10	Explain how the study size was arrived at	4
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	4,5,6
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	5,6
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	5,6
Statistical methods	#12c	Explain how missing data were addressed	5,6 upon request of reviewer 2
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	6,7
Statistical methods	#12e	Describe any sensitivity analyses	n/a
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give	3,4, upon request of reviewer 2

		information separately for exposed and unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	4
Participants	#13c	Consider use of a flow diagram	4
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	7,8
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	n/a. We excluded missing data before descriptively analysing the study population
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	7,8,9,10
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	7,8,9,10
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make	7,8,9,10,11

		clear which confounders were adjusted for and why they were included	
Main results	#16b	Report category boundaries when continuous variables were categorized	7,8,9,10,11
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	#18	Summarise key results with reference to study objectives	12
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	16
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	12,13,14,15
Generalisability	#21	Discuss the generalisability (external validity) of the study results	15,16

Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

Notes:

- 6b: n/a. The resent study does not contain matched studies
- 14b: n/a. We excluded missing data before descriptively analysing the study population
- 20: 14,15,16,17 The STROBE checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 16. August 2022 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Initial prescriptions and medication switches of biological products: an analysis of prescription pathways and determinants in the Swiss healthcare setting

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Initial prescriptions and medication switches of biological products: an analysis of prescription pathways and determinants in the Swiss healthcare setting

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ABSTRACT

Objectives Biological products have contributed to extraordinary advances in disease treatments over the last decade. However, the cost-saving potential of imitator products, so-called biosimilars, is still under-researched in Switzerland. This study aims to assess biosimilars' prescriptions at treatment initiation and their determinants, as well as biological therapy switches.

Design The study included all patients who had at least one biosimilar available on the market at the time when they were prescribed a biologic product. We analyzed longitudinal data for biosimilar prescriptions in Switzerland using descriptive statistics and logistic regression to quantify the associations with individual, pharmaceutical, and provider-related variables.

Setting The analysis is based on de-identified claims data of patients with mandatory health insurance at Helsana, one of the Swiss health insurances with a substantial enrollee base in mandatory health insurance.

Participants Overall, 18,953 patients receiving at least one biological product between 2016 and 2021 were identified.

Outcome measures: We differentiated between initial prescriptions and follow-up prescriptions. Our regression focused on initial prescriptions due to evidence indicating that patients tend to follow the medication prescribed at therapy initiation.

Results Although biosimilars market share was low (28.6%), the number of prescriptions has increased (from 1016 in 2016 to 6976 in 2021). Few patients with medication switches (n=1492, 8.5%) were detected. Increased relative price difference (difference in the price of available biosimilars relative to price of corresponding reference product) was associated with decreased probability of biosimilar prescriptions, whereas male sex, an increase of available imitator drugs on the market and, larger packaging sizes, and prescriptions from specialists or physicians in outpatient settings were associated with increased biosimilars use.

Conclusion The low number of biosimilar prescriptions despite the proliferating biosimilar market indicates a high potential for biosimilar diffusion. The findings indicate that patients typically adhere to the therapy options initially chosen and are less inclined to make changes following the initiation of treatment. Our research highlights the need for awareness initiatives to improve understanding among patients and physicians, enabling informed, shared decision-making about biosimilar prescriptions.

Keywords: biosimilars, biologics, reference products, switches, initial prescription

Strengths and limitations of this study

- This study evaluated the prescription of biosimilars using a broad set of sociodemographic, pharmaceutical, and healthcare provider variables and utilizing a nearly representative database in Switzerland.
- The study divided the medication treatment pathway into initial and follow-up prescriptions, with a specific focus on the initial prescriptions.
- The study assessed determinants of initial prescriptions in the context of biosimilars.
- Some demand-related factors (patients' health status, beliefs, and experiences) and supply-related factors (physicians' incentives and beliefs) about biosimilars could not be accounted using the claims data.

INTRODUCTION

Biological products increased the spectrum of available treatment options considerably in the treatment of many cancers and autoimmune diseases. However, these medications are more expensive compared to many conventional synthetic drugs as they are produced by living cells and, thus, require a more complex manufacturing process. Currently, there are a considerable number of biologics in the final stages of development and approval [1, 2]. The healthcare systems are likely to incur substantial costs even if just a small proportion of these biologics is granted market approval. One lever to curb rising drug costs is the replacement of biologics after patent expiration with less expensive imitator products, also known as biosimilars. Due to the biotechnological manufacturing process, exact copies of the biological products are not achievable. As a result, minor structural deviations in the biosimilar are unavoidable [3, 4], and regulatory authorities accept them for market approval [5, 6].

A study conducted in the United States found that biologics can undergo price reductions ranging from -2.4% to -59.3% in response to biosimilar competition, with the extent of these

reductions correlating with the adoption rate of biosimilars [7]. In Switzerland, a Swiss report has estimated a cost saving potential of over 60 million Swiss francs for the complete replacement of reference products with biosimilars in 2019 [8]. In the coming years, cost saving potential will increase as several top-selling biologics will lose their patent protection in Switzerland [8, 9] and corresponding biosimilars have already been approved in the European Union (EU) [2, 10, 11]. However, the realization of the cost saving potential us is assumed to be curbed because of skepticism about biosimilars from both the patient and physician side [12–15]. At the same time, patients and their health care providers seem to be less willing to switch biological products when therapy has already been started [16–20]. Consequently, the choice of initial prescription (IP) at therapy initiation is the decisive factor for following medication prescriptions. Despite the significant role of IP in shaping subsequent treatment pathways, research on the prescription behavior of biological products at therapy initiation and the impact of IP is limited. Existing studies have only demonstrated that patients tend to remain on their initial biological treatment product once medication treatment has been initiated [21]. Thus, there is a need for further investigation into the influencing factors of IP and their influence on the choice of medication path. Thus, this study aims to assess biosimilars' prescriptions at treatment initiation and their determinants, as well as biological therapy switches.

METHODS

Study design and population

We studied adult patients (≥18 years) with at least one biological product claim between 2016 and 2021, insured by Helsana Group, a major Swiss health insurer. (Table A1 in supplementary file). The Helsana database covers 15% of Switzerland's population (1.2 million residents) and

is regarded as representative, as prior research found minor differences between raw and adjusted results [22, 23].

In Switzerland, medication reimbursement is governed by the Federal Law on Health Insurance, which mandates that basic health insurance must cover the costs of essential medications. Swissmedic regulates the market entry of medications, while the Federal Office of Public Health oversees the establishment of the reimbursement list, which determines the extent to which a medication is reimbursed. Switzerland's medication reimbursement system aims to balance access to essential medications with cost control: To be eligible for reimbursement, medications must demonstrate efficacy, safety, and cost-effectiveness compared to standard treatments. As such, all of the biological products included in this study are presumed to have fulfilled these requirements.

Measures

The study included all patients who had at least one biosimilar available on the market at the time of IP of a biologic product. This enabled us to explore the determinants of non-prescription of biosimilars despite their availability. IP were defined for each patient as claims that were not preceded by other prescriptions in the same medication category within the previous 24 months. Prescriptions that followed within 12 months were labeled as “follow-up prescriptions” (FP). By restricting the follow-up period to 12 months, we were able to focus on the medications that were prescribed as a result of the initial prescription rather than medications that were prescribed for unrelated reasons. This approach allowed us to evaluate the impact of the initial prescription more accurately on subsequent medication use. We selected 117 biological products approved by Swissmedic from a list (Table A1 in supplementary file) derived from the Swiss Drug Compendium.

We considered patient characteristics as covariates, including sex, age group (<50, 50-64, 65-74, >74) and language region (German, French, Italian). We assessed comorbidity using the number of Pharmaceutical Cost Groups (PCG) per patient (0,1,2,>2). PCGs are a recognized proxy for the presence of chronic diseases using data on medications bills that were reimbursed [24]. The Swiss healthcare system offers different cost-sharing options to patients, including low (CHF 500, 1000) or high deductibles (i.e., CHF 1500, 2000, or 2500), and integrated care models, which offer premium rebates in exchange for limited healthcare provider options. Thus, having a low (CHF 500, 1000) or high deductible (i.e., CHF 1500, 2000, or 2500 vs. CHF 300), and being enrolled in a managed care model were used in the analysis. Prescribed medications were characterized by category (fusion proteins, hormones, monoclonal antibodies, low-molecular-weight [LMW] heparins and growth factors), whether there were multiple packaging sizes, the cost per package of the reference product (in CHF, <100, 100-599, >600), relative price difference of the reference product to the corresponding biosimilar (<10, 10-19, >20), and the number of available imitator drugs (1, 2, >2) at the date of prescription. The analysis adds the aspect of healthcare provider by including information on the supply channel (general practitioner, outpatient hospital, specialist, traditional pharmacy).

To ensure consistent terminology, we referred to all biologically manufactured drugs as "biological products", while the originator drugs are referred to as "biologics" or as "reference products", and imitator products as "biosimilars" throughout the manuscript.

Statistical analysis

All statistical analysis were performed at the study population that consisted of individuals who had at least one biosimilar available on the market at the time of IP of a biologic product. All research participants' baseline characteristics are shown as counts and percentages, or as mean and standard deviation for continuous variables. We compared patient characteristics for all

individuals with and without biosimilar IP. For bivariate comparisons between patients with and without biosimilar IP, Fisher exact and Chi-Square tests were used accordingly. Statistical significance was defined as a two-sided p-value of 0.05. We determined the biosimilar prevalence by distinguishing between IP and FP and the prevalence of biological therapy switches (number of prescriptions and patients) for each year (2016-2021). Chi-squared tests were used to determine whether the prevalence of biosimilars among all patients using a biological product was equivalent across the years. To assess the determinants of biosimilar prescriptions, we used logistic regression models in which the dependent variable was whether a biosimilar was prescribed as IP (0 or 1). We employed three distinct logistic regression models, each incorporating an additional set of variables, to comprehensively assess the impact of various factors on our study outcomes (Table A8 in supplementary file). This approach allows us to explore multiple dimensions of influence and gain a more nuanced understanding of the relationships at play, enhancing the robustness and depth of our analysis. Both, Model B (sociodemographic + medication variables) and C (sociodemographic + medication + provider variables), show similar results and a better fit of the estimates compared to Model A (sociodemographic variables) based on the goodness-of-fit criteria (AIC, BIC). For the manuscript, we proceed with Model C because we are mainly interested in the associations with biosimilar prescriptions from all three points of view (patient, medication, physician). Odds ratios (OR) and corresponding 95% confidence intervals (CI) were calculated for each regression coefficient. The success rate in the binomial model was denoted by the term "occurrence" to improve the results' readability. All analyses were performed using R version 4.2.1.

Patient and public involvement

None.

RESULTS

This research was conducted using a study population comprising 68,310 individuals who received at least one prescription for a biological or biosimilar medication between 2016 and 2021. For our study, we eliminated individuals who did not maintain continuous mandatory health insurance coverage throughout the entire observation period. This exclusion was implemented to mitigate potential bias in our regression analysis, resulting in a remaining sample size of 53,379 patients. Within this subgroup, there were 18,953 instances of initial prescriptions for biological medications that had a biosimilar alternative available at the time of dispensing.

In the study sample we observed 18,953 first prescriptions of biological products. Patient characteristics of the study population at the time of IP, stratified by type of IP (reference product 81.5%, biosimilar 18.5%), are presented in Table 1. Female patients more frequently received biosimilars than males (60.6%). The study's overall population demonstrated a balanced distribution among age categories (<50, 50-64, 65-74, >74). Notably, individuals prescribed reference products as IP were more prevalent in the highest age group, while those initially prescribed biosimilars were more concentrated in the 50-64 and 65-74 age group. LMW heparins were the most prescribed reference products (54.2%), with growth hormones constituting the largest group of biosimilars (57.9%).

Table 1. Comparison of patient characteristics at IP between patients with reference product and biosimilar as IP

Variables, n (%)	Total	Patients with IP = Reference product	Patients with IP = Biosimilar	p-value
Observations	18,953	15,453 (81.5%)	3500 (18.5%)	
Sex				
Male	7275 (38.4%)	5895 (38.1%)	1380 (39.4%)	[1]
Female	11,678 (61.6%)	9558 (61.9%)	2120 (60.6%)	[1]
Age group				*** [2]
<50 years	5501 (29.0%)	4613 (29.9%)	888 (25.4%)	
50-64 years	4720 (24.9%)	3764 (24.4%)	956 (27.3%)	

65-74 years	3963 (20.9%)	3001 (19.4%)	962 (27.5%)	
>74 years	4769 (25.2%)	4075 (26.4%)	694 (19.8%)	
Language region				*** [2]
German	12,719 (67.1%)	9958 (64.4%)	2761 (78.9%)	
French	4324 (22.8%)	3777 (24.4%)	547 (15.6%)	
Italian	1910 (10.1%)	1718 (11.1%)	192 (5.5%)	
Number of comorbidities				** [2]
0	4738 (25.0%)	3901 (25.2%)	837 (23.9%)	
1	3295 (17.4%)	2664 (17.2%)	631 (18.0%)	
2	3072 (16.2%)	2448 (15.8%)	624 (17.8%)	
>2	7848 (41.4%)	6440 (41.7%)	1408 (40.2%)	
Deductible				*** [2]
Low	15,765 (83.2%)	12,846 (83.1%)	2919 (83.4%)	
High	3188 (16.8%)	2607 (16.9%)	581 (16.6%)	
Managed care	11,921 (62.9%)	9790 (63.4%)	2131 (60.9%)	** [1]
Category				*** [2]
Fusion proteins	360 (1.9%)	178 (1.2%)	182 (5.2%)	
Hormones	2112 (11.1%)	1697 (11.0%)	415 (11.9%)	
Monoclonal antibodies	2908 (15.3%)	2107 (13.6%)	801 (22.9%)	
LMW heparins	10,272 (54.2%)	10,196 (66.0%)	76 (2.2%)	
Growth factors	3301 (17.4%)	1275 (8.3%)	2026 (57.9%)	
Multiple package size	16,432 (86.7%)	13,532 (87.6%)	2900 (82.9%)	*** [2]
Cost per package of reference product (in CHF)				*** [2]
<100	9866 (52.1%)	9652 (62.5%)	214 (6.1%)	
100-599	5066 (26.7%)	3179 (20.6%)	1887 (53.9%)	
>600	4021 (21.2%)	2622 (17.0%)	1399 (40.0%)	
Relative price difference (%)				*** [2]
<10	13,807 (72.8%)	11,546 (74.7%)	2261 (64.6%)	
10-19	2386 (12.6%)	1871 (12.1%)	515 (14.7%)	
>20	2760 (14.6%)	2036 (13.2%)	724 (20.7%)	
Number of available imitator drugs				*** [2]
0	-	-	-	
1	12,490 (65.9%)	12,012 (77.7%)	478 (13.7%)	
2	2741 (14.5%)	1911 (12.4%)	830 (23.7%)	
>2	3722 (19.6%)	1530 (9.9%)	2192 (62.6%)	
supply channel of first prescription				*** [2]
General practitioner	1185 (6.3%)	1097 (7.1%)	88 (2.5%)	
Outpatient hospital	6224 (32.8%)	4359 (28.2%)	1865 (53.3%)	
Specialist	3606 (19.0%)	2674 (17.3%)	932 (26.6%)	
Traditional pharmacy	7564 (39.9%)	6981 (45.2%)	583 (16.7%)	
Rest	374 (2.0%)	342 (2.2%)	32 (0.9%)	

[1]) Fisher exact test, [2]) Chi-Square test

Signif. codes: '***' 0.001

Table 2 describes the overall frequency of biologicals products over the observation period including the absolute and relative frequency of biosimilars in comparison to all biological prescriptions. Of all biological products (IP and FP), 28.6% were biosimilar prescriptions. In absolute values, the prescription rate of biosimilars increased over time (from 1016 in 2016 to 6976 in 2021). However, there is no discernible trend in the relative share of biosimilars in all prescriptions of biological products (35.5% in 2016, 39.2% in 2017, 45.2% in 2018, 41.6% in 2019, 26.3% in 2020 and 22.5% in 2021). Furthermore, the share of biosimilars in FPs was higher than in IPs in every year. The growth factor Filgrastim was the most frequently prescribed active substance of biosimilars in IPs and FPs (53.1% and 36.2% respectively), while enoxaparin was the most frequently prescribed active substance of reference products in IPs and FPs (65.3% and 25.5%, respectively) (Table A2-A6 in supplementary file).

Table 2. All prescriptions for which a biosimilar was approved at the time of the prescription

	total	2016	2017	2018	2019	2020	2021	
IP								
n	18,953	815	888	1037	1520	5313	9380	
Biosimilars (n, % of N)	3500 (18.5%)	262 (32.1%)	343 (38.6%)	391 (37.7%)	612 (40.3%)	813 (15.3%)	1079 (11.5%)	*** [1]
FP								
n	50,251	2047	2716	3314	6306	14,288	21,580	
Biosimilar (n, % of N)	16,293 (32.4%)	754 (36.8%)	1071 (39.4%)	1578 (47.6%)	2644 (41.9%)	4349 (30.4%)	5897 (27.3%)	*** [1]
Total (FP+IP)								
n	69,204	2862	3604	4351	7826	19,601	30,960	
Biosimilars (n, % of N)	19,793 (28.6%)	1016 (35.5%)	1414 (39.23%)	1969 (45.25%)	3256 (41.60%)	5162 (26.34%)	6976 (22.53%)	*** [1]

[1] Chi-Square test, Signif. codes: '***' <0.001

Of the study population, only a small subset (n=1492, 8.5%) experienced at least one medication switch (Table 3). Most patients had switches between reference products (n=867, 58.1%), followed by switches from reference product to biosimilar (n=331, 22.2%), from biosimilar to reference product (n=297, 19.9%) and switches between biosimilars (n=286, 19.2%). The number of patients with at least one switch increased between 2016 and 2021

(from 28 to 662), whereby the numbers of patients with switches between reference products increased most prominently (from 25.0% in 2016 to 62.1% in 2021). Switches between reference products and between biosimilars occurred most often for Enoxaparin and Rituximab, respectively (Table A7 in supplementary file). The most common switches from reference product to biosimilar and from biosimilar to reference products were most often observed for Filgrastim and Enoxaparin.

Table 3. Patients with biologic therapy switches

Switches, N=patients	Total	2016	2017	2018	2019	2020	2021	p-value
At least one, n	1492	28	42	77	249	434	662	
Reference Prod to Reference Prod, n (%)	867 (58.1%)	7 (25.0%)	15 (35.7%)	37 (48.1%)	146 (58.6%)	251 (57.8%)	411 (62.1%)	***[1]
Biosimilar to Biosimilar, n (%)	286 (19.2%)	9 (32.1%)	10 (23.8%)	14 (18.2%)	51 (20.5%)	74 (17.1%)	128 (19.3%)	[1]
Reference Prod to Biosimilar, n (%)	331 (22.2%)	6 (21.4%)	11 (26.2%)	21 (27.3%)	60 (24.1%)	103 (23.7%)	130 (19.6%)	[1]
Biosimilar to Reference Prod, n (%)	297 (19.9%)	10 (35.7%)	8 (19.0%)	15 (19.5%)	49 (19.7%)	96 (22.1%)	119 (18.0%)	[1]

[1]) Chi-Square test
Signif. codes: '***' <0.001

As far as the regression results are concerned, the odds of prescribing biosimilars at IP have been increasing over the years (Fig.1, Table A8 in supplementary file). Male sex was associated with 13.2% higher odds of receiving biosimilar IP, whereas residence in a French or Italian-speaking region had a 38.9% and 23.9%, respectively, lower occurrence of a biosimilar IP. None of the insurance-related variables showed a significant association with biosimilars IPs. In terms of pharmaceutical variables, monoclonal antibodies, LMW heparins and growth factors were associated with substantially lower biosimilar IP occurrences (-88.5%, -99.9% and -84.2%) than fusion proteins. The availability of multiple packaging sizes was associated with 4.6-fold higher odds of biosimilar IP compared to medications with solely one packaging size. For the absolute package price, no consistent pattern was observed, as medications with prices

between 100 and 599 francs per pack decreased the odds by 79.8% compared to the baseline (<100 CHF), whereas the odds in the highest prize category (>600 CHF) were lower by 34.3%. However, compared to products with a <10% price difference between reference product and biosimilar, higher price reductions were associated with decreased occurrence of biosimilar IP: medications with 10-19% price difference had 92.4% lower odds and medications with more than 20% had even 93.3% lower odds. On the contrary, increasing the number of available imitator medications of prescription (2 and >2) had substantially higher (2.36-fold and 9.65-fold) odds of biosimilar IP compared to prescriptions with only one available biosimilar. As far as provider variables are concerned, physicians in the outpatient hospital setting prescribed far more biosimilars compared to general practitioners (2.48-fold higher odds). The occurrence of biosimilar IP was also 41.7% higher in patients who had been prescribed biological products by a specialist than in patients who had received the equivalent medications from a general practitioner.

DISCUSSION

The increase in biosimilar prescriptions over time can be attributed to the growing biosimilar market. With 15 approved biosimilars in 2016, this market has expanded significantly, reaching 78 biosimilars in 2021 (Table A1 in supplementary file) [8, 21]. A longer time on the market gives the biosimilar a better chance to establish itself and gain market share. Despite this growth, the biosimilars' claims in Switzerland remained relatively low. In 2021, claims for reference products were four times higher than claims for biosimilars among all available biological products with biosimilars. [8]. Comparatively, other countries like Norway have achieved 80% biosimilar quota of all biologic products[25], while in Germany, studies reported an average biosimilar ratio between 40.5% and 51.9% in 2019[26, 27]. In the present study we observed substantially lower average biosimilar quota of 28.0%. Infliximab is a particularly

compelling example, with the biosimilar share reaching 26% in Germany after only 12 months on the market (2017) and rising to 64-68% of the biosimilar market in 2019. By contrast, infliximab achieved a market share of only 22% in Switzerland in 2019 [8].

The low biosimilar market share in Switzerland can be attributed to several factors, including physician and patient knowledge deficits regarding biosimilars, leading to reluctance in their use [12–15]. According to survey studies [20, 28–31], negative perceptions of biosimilars among 15-30% of the population may be rooted in concerns about the evidence base for their efficacy and safety, primarily requiring bioequivalence for approval.. However, there is increasing evidence of equivalent safety and efficacy of biosimilars, along with evidence of bioequivalence [32–34]. Furthermore, a challenge for newly approved biosimilars is the difficulty in extending conclusions from RCTs to the broader population that will use the biosimilar. This is because RCTs typically enroll a more homogeneous population, and certain patient groups, such as pediatric, elderly, and comorbid populations, as well as patients with polypharmacy, are often underrepresented in these trials [35–37]. As a result, prescribers may be skeptical about the use of biosimilars in these patient populations because of the lack of data. Moreover, the finding that patients frequently switch from biosimilar to reference products underscores the complex landscape surrounding biosimilar utilization. This phenomenon may, in part, be influenced by the current incentive system discourages the prescription of biosimilars for self-dispensing doctors and pharmacies as they are rewarded with larger profit margins for prescribing the more expensive products [8]. Conversely, under a capitation payment model, managed care physicians may have a financial incentive to prescribe lower-cost biosimilars in order to maximize profits. However, if physicians are not properly educated about the safety and efficacy of biosimilars, they may be hesitant to prescribe them.

That only a small subset (n=1492, 8.5%) experienced at least one medication switch can be explained by the reluctance of patients to switch to a biosimilar medication due to the fear of

experiencing new and unknown side effects. Patients who have been using a particular medication for a long time and have become accustomed to its efficacy and safety profile may be hesitant to switch to a biosimilar, which they perceive as being different and possibly inferior. Nevertheless, efficacy of biosimilar switching has been observed [8, 32–34, 38, 39]. According to a systematic literature review based on 90 published studies, the great majority of the publications did not report differences in immunogenicity, safety, or efficacy when patients switched to biosimilars. Three large studies did not show differences in efficacy or safety after multiple switches between reference product and biosimilar [40–42]. Only two publications reported a loss of efficacy or increased dropout rates [43, 44]. Often, this very knowledge and awareness about the safety and efficacy of switching to new treatment options lack for prescribing physicians who rely on solid, evidence-based data to make treatment decisions [45–47]. The substantial transition from biosimilars to reference products observed in our study warrants discussion. While our analysis didn't delve into the specific drivers behind this shift, several factors may contribute to it. These could encompass the beforementioned patient and physician preferences. Further exploration of these factors is essential to gain a comprehensive understanding of the dynamics between biosimilars and reference products in clinical practice, shedding light on the implications for healthcare stakeholders and policymakers.

The regression results revealed that biosimilar IP rates were lower in French-speaking cantons. These regional variations may be caused by a variety of variables, including a higher concentration of medical services in urban regions, various patient characteristics, and cultural variations between cantons [48, 49]. Our findings showed that biosimilars with high relative price difference to reference product were less likely prescribed. Several factors contribute to physicians' reduced prescription rates in association with the lower prices of biosimilars. A possible explanation is that healthcare providers may have less experience with biosimilars with a higher price difference or may perceive them as less established and less proven than

biosimilars with a lower price difference. This lack of familiarity or perceived risk may contribute to reluctance in prescribing biosimilars with a higher price difference. It is also important to consider the role of financial incentives and reimbursement policies in biosimilar prescribing: Currently, dispensation channels receive a larger profit margin when distributing the more expensive reference product under the present price-dependent margin [21]. This incentive system seems to be characteristic for Switzerland, as studies conducted in European countries did not find a relationship between price difference and biosimilar dissemination [50–52]. This might be attributed to several factors that differentiate Switzerland from other European countries: Cantonal differences in self-dispensing regulation, the country's different prescribing cultures and guidelines across its language regions, and capitation is implemented only in relatively few cases in Switzerland. In our analysis, male patients had more biosimilar IP. According to studies, women were often more skeptical of imitator drugs [28, 53–56] and they more frequently believe that they are more responsive to medications than men [57–59]. This can have an impact on their confidence in biosimilars, making female patients more aware of potential side effects or lack thereof. Biosimilar IPs were prescribed more frequently for fusion proteins compared to other categories which indicates an increased acceptance of imitator products in this drug class. This is supported by the relatively early market entry (2018) and by a meta-analysis showing comparable results in terms of efficacy and safety between reference product and biosimilars [60]. The strongest facilitator of biosimilar prescriptions was the amount of available biosimilars, which is in line with the findings of a prior study [50, 61]. Thus, the replacement of reference products by biosimilars seems to be better accepted in market segments with many imitator products. This finding is probably associated with the larger collective promotional effort from multiple players involved in the field to favor biosimilars; it is noteworthy that the largest adoption of biosimilars (Filgrastim) has been partially attributable to the fact that numerous biosimilar producers have commercialized

different products, whereas there is only one company branding the reference product [62]. We found more biosimilar IPs for specialists and outpatient hospital physicians than GP. These findings are in line with existing literature that showed more biosimilars from specialists who reported a higher confidence in the comparability of biosimilars than GPs [63, 64]. Differences in care providers may be due to a variety of reasons: some healthcare providers may not be interested in stockpiling too many different medications and additional biosimilars, as they sometimes have large storage requirements (cooling, expiration date) and , thus, are associated with a significant financial risk [21]. In addition, it has been demonstrated that the dissemination of knowledge about new prescription options is heterogeneous because there are large learning costs associated with the treatment effects of new therapy options, which rely on the training and experience of the doctor [65]. Despite the fact that a previous study conducted in the context of generic drugs showed that older people are less likely to use imitator products when offered a choice [28, 61], we did not observe an age-dependency of biosimilar prescriptions.

The most valuable strength of this study is the extensive dataset of biosimilar prescriptions and potential influencing factors including sociodemographic, pharmaceutical and healthcare provider variables that were gathered from a representative sample of the Swiss population. Hence, earlier research has suggested that this database can be considered reasonably representative of the broader Swiss population, given that the findings revealed only minimal disparities between unadjusted and adjusted results. The main limitation is the dearth of clinical data in our database (e.g., disease severity, clinical diagnosis, and reason for biosimilar utilization). However, we attempted to mitigate this by utilizing comorbidity measures based on reimbursed prescriptions to control for potential confounders. Furthermore, it is possible that invoices from individuals whose annual healthcare expenses did not surpass the annual deductible were not included in the analysis. Nevertheless, internal analyses conducted by Helsana indicated that this proportion accounts for approximately 1.5% of invoices, suggesting

that any potential selection bias is likely minimal. Another limitation of our study is that the follow-up period for the prescriptions was limited to 12 months. This time frame may have led to the exclusion of some prescriptions, potentially introducing bias into our results. Nevertheless, we observed that a significant number of patients (7608, which accounts for 43.1% of the total) were given only one prescription, indicating that any bias arising from this limitation is expected to be insignificant.

It is worth noting that the actual biosimilars quota (proportion of biosimilars claims relative to overall biological product claims), is lower in reality as there are biological products for which no corresponding biosimilars are available on the market. Nevertheless, even when considering this relatively higher observed quota, it remains comparatively low compared to other EU countries. This has important implications for the adoption and utilization of these products in Switzerland. Patients and physicians should be better and objectively informed about biosimilars in order to increase the acceptance [47, 48]. Also, for example, a clear and conspicuous indication of the prescribed active substance on the medication package for both the reference product and the imitator drug, for instance, could enhance patient confidence [42]. To address the perceived uncertainty and mistrust in imitator products, the evidence base should be further strengthened: direct evidence to help explain some of the practical aspects related to the use of biosimilars can be provided by retrospective studies, national databases and registries that track the long-term immunogenicity and safety of biosimilars [66–71]. In addition, the incentive system for healthcare providers seems to be designed in such a way that fewer biosimilars are prescribed. Thus, these incentives should be eliminated, for example by introducing a fixed margin that always remunerates the medication supplier the same regardless of the prescribed product (reference product or biosimilar). In order to exploit the cost saving potential of biosimilars, the aforementioned measures should be targeted to biosimilars with a noticeable price difference compared to their reference products, and that

still possess relatively low biosimilar market share. Taking into account the findings presented in Table A6 (in supplementary file), notable examples of these biosimilars include bevacizumab, follitropin alfa, and pegfilgrastim.

However, the decision to prescribe an imitator drug should not merely be motivated by the cost-saving potential but should ensure appropriate health care provision for the patients. Therefore, it is crucial for healthcare providers to engage in shared-decision making with their patients to determine the most appropriate treatment option based on their individual medical situation.

CONCLUSION

Despite an increase of available biosimilars in Switzerland between 2016 and 2021, the biosimilars market share remained relatively low over time. In addition, biological therapy switches were rarely observed, highlighting the importance of IPs. Our study suggests that greater acceptance and higher utilization of biosimilars may be associated with the availability of different package sizes and lower price differences between biosimilars and their reference products. Patients and providers should be informed about biosimilars in a timely and appropriate manner, and outdated incentive structures have to be changed to increase the use of biosimilars.

*** ***

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Contributors KW, MN and CH designed the study. MN did data preparation and data management. MN and KW performed the statistical analyses, with the contribution of SB, CH and EB. KW drafted the main manuscript text. All authors assisted in the interpretation of the results and critically revised the manuscript. All authors have read and approved the manuscript.

Data availability statement Helsana provides the data that support up the findings of this research. (https://www.helsana.ch/en/helsana-group). These data, which were used under license for the present study and are not accessible to the general public, are subject to restrictions. But with Helsana's consent and upon reasonable request, data are available from the authors (gesundheitskompetenz@helsana.ch).

Ethics approval The data used in this study were retrospective, pre-existing, de-identified, and anonymous in accordance with privacy laws and regulations. This study was free from the provisions of the Swiss Federal Law on Human Research because it used retrospective, de-identified, and anonymized data (Humanforschungsgesetz) [72] and was thus exempted from receiving clearance from the regional ethics committee (the ethical committee of the Canton of Zurich) as well as from obtaining the patients' informed consent.

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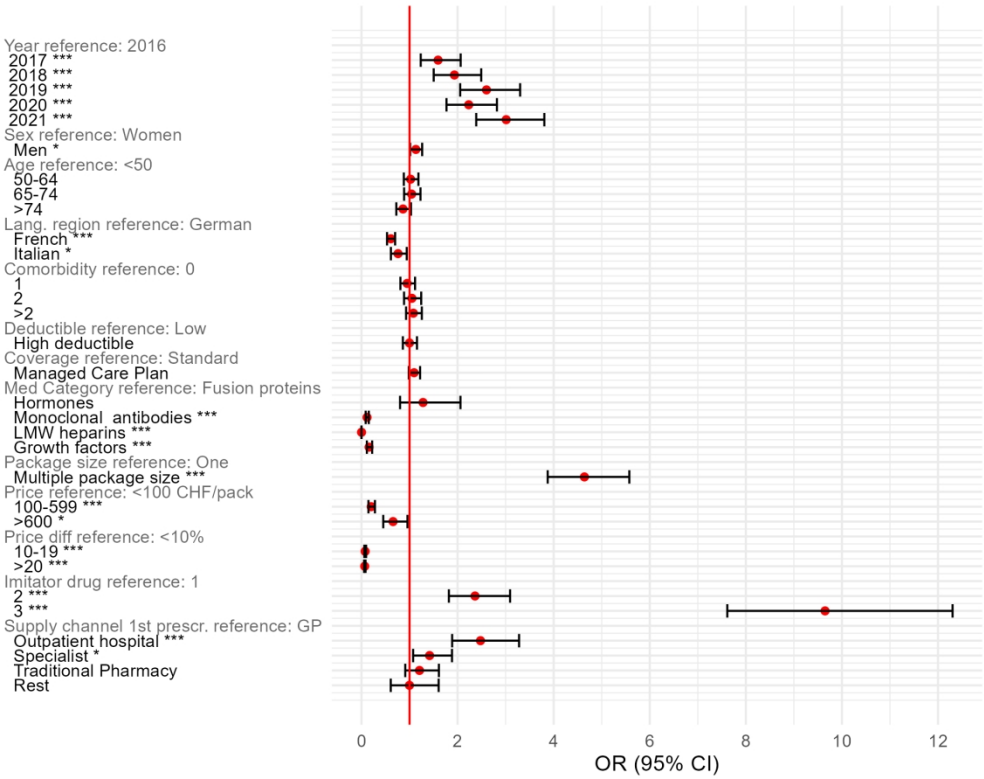
FIGURE TITLE

Figure 1. Determinants of biosimilar initial prescription (logistic regression)



177x140mm (300 x 300 DPI)

Table A1 Substitution catalogue: reference product & biosimilar (2016-2021)

ATC	Reference Product			Biosimilar			
	medication	Dose (mg) / unit	cost (in CHF)	medication	Reimburment date	Dose (mg) / unit	cost (in CHF)
Low-molecular-weight heparins							
B01	Clexane	20 / 10	41	Inhixa	01.08.2020	20 / 10	38.55
B01	Clexane	20 / 50	139.55	Inhixa	01.08.2020	20 / 50	127.25
B01	Clexane	40 / 2	17.35	Inhixa	01.08.2020	40 / 2	16.45
B01	Clexane	40 / 10	62.45	Inhixa	01.08.2020	40 / 10	57.85
B01	Clexane	40 / 50	246.75	Inhixa	01.08.2020	40 / 50	223.7
B01	Clexane	60 / 10	76.65	Inhixa	01.08.2020	60 / 10	70.6
B01	Clexane	80 / 10	102.3	Inhixa	01.08.2020	80 / 10	93.7
B01	Clexane	100 / 10	123.75	Inhixa	01.08.2020	100 / 10	113
B01	Clexane	120 / 10	134.9	Inhixa	01.08.2020	120 / 10	123.05
B01	Clexane	150 / 10	161.3	Inhixa	01.08.2020	150 / 10	146.8
B01	Clexane	300 / 1	41.3	Inhixa	01.08.2020	300 / 1	38.8
Growth factors							
L03	Neupogen	0.3 / 5	531.1	Accofil	01.11.2019	0.3 / 5	479.65
				Filgrastim-Teva	01.03.2010	0.3 / 5	479.65
				Zarzio	01.05.2010	0.3 / 5	479.65
L03	Neupogen	0.48 / 5	740.9	Accofil	01.11.2019	0.48 / 5	668.45
				Filgrastim-Teva	01.03.2010	0.48 / 5	668.45
				Zarzio	01.05.2010	0.48 / 5	668.45
L03	Neulasta	6 / 1	1668.75	Grasustek	01.09.2021	6 / 1	1266.95
				Pelgraz	01.11.2019	6 / 1	1266.85
				Pelgraz	01.11.2019	6 / 1	1266.85
				Pelmeg	01.01.2020	6 / 1	857.55
				Ziextenzo	01.03.2020	6 / 1	1266.95
				Fulphila	01.06.2020	6 / 1	1266.85
B03	Eprex	0.008 / 6	71.5	Binocrit	01.10.2009	0.008 / 6	66.15
B03	Eprex	0.017 / 6	126.55	Binocrit	01.10.2009	0.017 / 6	115.7
B03	Eprex	0.025 / 6	181.65	Binocrit	01.10.2009	0.025 / 6	165.25
B03	Eprex	0.037 / 6	236.75	Binocrit	01.10.2009	0.037 / 6	214.7
B03	Eprex	0.046 / 6	291.8	Binocrit	01.10.2009	0.046 / 6	264.5
B03	Eprex	0.092 / 6	567.2	Binocrit	01.10.2009	0.092 / 6	512.1
Hormones							
A10	Lantus	10.9 / 5	81.85	Abasaglar	01.09.2015	10.9 / 5	68.4
G03	GONAL-F	0.022 / 1	156.4	Ovaleap	01.11.2018	0.022 / 1	122.05
G03	GONAL-F	0.033 / 1	226.45	Ovaleap	01.11.2018	0.033 / 1	174.95

G03	GONAL-F	0.066 / 1	430.65	Ovaleap	01.11.2018	0.066 / 1	329.1
H01	Genotropin	5 / 1	221.65	Omnitrope	01.11.2010	5 / 1	201.1
H01	Genotropin	5 / 5	1041.9	Omnitrope	01.11.2010	5 / 5	940
H05	Forsteo	0.25 / 1	412.75	Movymia	01.09.2019	0.25 / 1	340.75
				Terrosa	01.09.2019	0.25 / 1	340.75
				Terrosa	01.09.2019	0.25 / 1	340.75
Fusion proteins							
L01	MabThera	100 / 2	627.3	Rixathon	01.09.2018	100 / 2	505.5
				Truxima	01.01.2019	100 / 2	505.5
L01	MabThera	500 / 1	1515.65	Rixathon	01.09.2018	500 / 1	1225.7
				Truxima	01.01.2019	500 / 1	1225.7
L01	Herceptin	150 / 1	686.4	Herzuma	01.12.2021	150 / 1	562.45
				Trazimera	01.10.2019	150 / 1	562.45
				Kanjinti	01.02.2020	150 / 1	562.45
				Ogivri	01.09.2020	150 / 1	562.45
L01	Herceptin	440 / 1	1932.85	Herzuma	01.12.2021	150 / 1	1586.75
				Trazimera	01.10.2019	150 / 1	1586.75
				Kanjinti	01.02.2020	150 / 1	1586.75
				Ogivri	01.09.2020	150 / 1	1586.75
L01	Avastin	100 / 1	410.65	Oyavas	01.08.2021	100 / 1	312.1
				Bevacizumab-Teva	01.07.2021	100 / 1	312.1
				MVASI	01.07.2020	100 / 1	312.1
				Zirabev	01.08.2020	100 / 1	312.1
L01	Avastin	400 / 1	1469.5	Oyavas	01.08.2021	400 / 1	1117.5
				Bevacizumab-Teva	01.07.2021	400 / 1	1117.5
				MVASI	01.07.2020	400 / 1	1117.5
				Zirabev	01.08.2020	400 / 1	1117.5
L04	Enbrel	25 / 4	682.35	Benepali	01.04.2019	25 / 4	515.8
				Erelzi	01.07.2018	25 / 4	515.8
L04	Enbrel	50 / 2	669.05	Benepali	01.04.2019	50 / 2	504.3
				Erelzi	01.07.2018	50 / 2	505.9
L04	Remicade	100 / 1	695.75	Inflectra	01.08.2016	100 / 1	627.25
				Remsima	01.01.2016	100 / 1	627.25
L04	Humira	20 / 2	661.8	Hyrimoz	01.11.2019	20 / 2	500.45
L04	Humira	40 / 1	661.8	Abrilada	01.06.2021	40 / 1	500.45
				Amgevita	01.11.2019	40 / 1	500.45
				Hyrimoz	01.11.2019	40 / 1	500.45
				Idacio	01.08.2020	40 / 1	500.45
				Imraldi	01.07.2020	40 / 1	498.55
				Hulio	01.08.2020	40 / 1	500.45

Table A2 First Prescriptions: Reference Products (active substance)

Active substance	total	2016	2017	2018	2019	2020	2021
n	14'987	433 (2.9%)	394 (2.6%)	501 (3.3%)	861 (5.7%)	4'525 (30.2%)	8'273 (55.2%)
Adalimumab	369 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	24 (2.8%)	182 (4.0%)	163 (2.0%)
Bevacizumab	267 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	96 (2.1%)	171 (2.1%)
Enoxaparin	9'785 (65.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3'047 (67.3%)	6'738 (81.4%)
Epoetin alfa	136 (0.9%)	20 (4.6%)	30 (7.6%)	19 (3.8%)	23 (2.7%)	24 (0.5%)	20 (0.2%)
Etanercept	176 (1.2%)	0 (0.0%)	0 (0.0%)	37 (7.4%)	55 (6.4%)	38 (0.8%)	46 (0.6%)
Filgrastim	658 (4.4%)	158 (36.5%)	134 (34.0%)	107 (21.4%)	85 (9.9%)	104 (2.3%)	70 (0.8%)
Follitropin alfa	747 (5.0%)	0 (0.0%)	0 (0.0%)	41 (8.2%)	182 (21.1%)	226 (5.0%)	298 (3.6%)
Infliximab	530 (3.5%)	141 (32.6%)	103 (26.1%)	74 (14.8%)	68 (7.9%)	68 (1.5%)	76 (0.9%)
Insulin glargin	640 (4.3%)	113 (26.1%)	127 (32.2%)	126 (25.1%)	102 (11.8%)	88 (1.9%)	84 (1.0%)
Pegfilgrastim	457 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	35 (4.1%)	225 (5.0%)	197 (2.4%)
Rituximab	661 (4.4%)	0 (0.0%)	0 (0.0%)	97 (19.4%)	203 (23.6%)	178 (3.9%)	183 (2.2%)
Somatropin	5 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	2 (0.0%)	0 (0.0%)
Teriparatid	304 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	55 (6.4%)	134 (3.0%)	115 (1.4%)
Trastuzumab	252 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	27 (3.1%)	113 (2.5%)	112 (1.4%)

Table A3 First Prescriptions: Biosimilars (active substance)

Active substance	total	2016	2017	2018	2019	2020	2021
n	3'489	261 (7.5%)	344 (9.9%)	393 (11.3%)	616 (17.7%)	809 (23.2%)	1'066 (30.6%)
Adalimumab	165 (4.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (1.1%)	63 (7.8%)	95 (8.9%)
Bevacizumab	28 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (0.6%)	23 (2.2%)
Enoxaparin	76 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (0.9%)	69 (6.5%)
Epoetin alfa	34 (1.0%)	8 (3.1%)	2 (0.6%)	7 (1.8%)	9 (1.5%)	3 (0.4%)	5 (0.5%)
Etanercept	185 (5.3%)	0 (0.0%)	0 (0.0%)	10 (2.5%)	49 (8.0%)	69 (8.5%)	57 (5.3%)
Filgrastim	1'854 (53.1%)	243 (93.1%)	271 (78.8%)	295 (75.1%)	342 (55.5%)	336 (41.5%)	367 (34.4%)
Follitropin alfa	219 (6.3%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	40 (6.5%)	71 (8.8%)	107 (10.0%)
Infliximab	281 (8.1%)	7 (2.7%)	31 (9.0%)	49 (12.5%)	54 (8.8%)	61 (7.5%)	79 (7.4%)
Insulin glargin	141 (4.0%)	0 (0.0%)	39 (11.3%)	29 (7.4%)	33 (5.4%)	21 (2.6%)	19 (1.8%)
Pegfilgrastim	129 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	32 (4.0%)	97 (9.1%)
Rituximab	318 (9.1%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	78 (12.7%)	120 (14.8%)	119 (11.2%)
Somatropin	5 (0.1%)	3 (1.1%)	1 (0.3%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Teriparatid	47 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.6%)	20 (2.5%)	23 (2.2%)
Trastuzumab	7 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	6 (0.6%)

Table A4 Rest prescriptions: Reference Products (active substance)

Active substance	total	2016	2017	2018	2019	2020	2021
n	33'958	1'293 (3.8%)	1'645 (4.8%)	1'736 (5.1%)	3'662 (10.8%)	9'939 (29.3%)	15'683 (46.2%)
Adalimumab	3'070 (9.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	41 (1.1%)	1'354 (13.6%)	1'675 (10.7%)
Bevacizumab	2'109 (6.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	481 (4.8%)	1'628 (10.4%)
Enoxaparin	8'669 (25.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2'343 (23.6%)	6'326 (40.3%)
Epoetin alfa	2'052 (6.0%)	234 (18.1%)	385 (23.4%)	408 (23.5%)	200 (5.5%)	422 (4.2%)	403 (2.6%)
Etanercept	791 (2.3%)	0 (0.0%)	0 (0.0%)	90 (5.2%)	310 (8.5%)	198 (2.0%)	193 (1.2%)
Filgrastim	2'252 (6.6%)	408 (31.6%)	428 (26.0%)	403 (23.2%)	275 (7.5%)	403 (4.1%)	335 (2.1%)
Follitropin alfa	1'914 (5.6%)	0 (0.0%)	0 (0.0%)	19 (1.1%)	502 (13.7%)	561 (5.6%)	832 (5.3%)
Infliximab	2'973 (8.8%)	543 (42.0%)	660 (40.1%)	424 (24.4%)	434 (11.9%)	435 (4.4%)	477 (3.0%)
Insulin glargin	1'036 (3.1%)	108 (8.4%)	170 (10.3%)	134 (7.7%)	443 (12.1%)	112 (1.1%)	69 (0.4%)
Pegfilgrastim	1'426 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	78 (2.1%)	699 (7.0%)	649 (4.1%)
Rituximab	3'148 (9.3%)	0 (0.0%)	0 (0.0%)	258 (14.9%)	1'177 (32.1%)	814 (8.2%)	899 (5.7%)
Somatropin	7 (0.0%)	0 (0.0%)	2 (0.1%)	0 (0.0%)	2 (0.1%)	3 (0.0%)	0 (0.0%)
Teriparatid	1'791 (5.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	79 (2.2%)	856 (8.6%)	856 (5.5%)
Trastuzumab	2'720 (8.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	121 (3.3%)	1'258 (12.7%)	1'341 (8.6%)

Table A5 Rest prescriptions: Biosimilars (active substance)

Active substance	total	2016	2017	2018	2019	2020	2021
n	16'293	754 (4.6%)	1'071 (6.6%)	1'578 (9.7%)	2'644 (16.2%)	4'349 (26.7%)	5'897 (36.2%)
Adalimumab	3'100 (19.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	64 (2.4%)	1'256 (28.9%)	1'780 (30.2%)
Bevacizumab	306 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	21 (0.5%)	285 (4.8%)
Enoxaparin	41 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.1%)	38 (0.6%)
Epoetin alfa	844 (5.2%)	32 (4.2%)	114 (10.6%)	257 (16.3%)	369 (14.0%)	55 (1.3%)	17 (0.3%)
Etanercept	930 (5.7%)	0 (0.0%)	0 (0.0%)	23 (1.5%)	247 (9.3%)	377 (8.7%)	283 (4.8%)
Filgrastim	5'894 (36.2%)	695 (92.2%)	752 (70.2%)	897 (56.8%)	1'110 (42.0%)	1'142 (26.3%)	1'298 (22.0%)
Follitropin alfa	583 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	74 (2.8%)	210 (4.8%)	299 (5.1%)
Infliximab	1'507 (9.2%)	23 (3.1%)	115 (10.7%)	274 (17.4%)	278 (10.5%)	374 (8.6%)	443 (7.5%)
Insulin glargin	509 (3.1%)	0 (0.0%)	80 (7.5%)	126 (8.0%)	143 (5.4%)	98 (2.3%)	62 (1.1%)
Pegfilgrastim	406 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	125 (2.9%)	281 (4.8%)
Rituximab	1'763 (10.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	356 (13.5%)	564 (13.0%)	843 (14.3%)
Somatropin	16 (0.1%)	4 (0.5%)	10 (0.9%)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
Teriparatid	297 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	114 (2.6%)	181 (3.1%)
Trastuzumab	97 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (0.2%)	87 (1.5%)

Table A6 Biosimilars quota by active substance

Active substance	Avg. relative Price difference	Biosimilars quota (IP+RP) 2016	2017	2018	2019	2020	2021
Adalimumab	24.63	-	-	-	52.21	46.2	50.5
Bevacizumab	23.98	-	-	-	-	4.31	14.62
Enoxaparin	7.77	-	-	-	-	<1	<1
Epoetin alfa	8.91	3.1	21.85	38.21	62.9	11.51	4.94
Etanercept	24.52	-	-	20.63	44.78	65.4	58.72

Filgrastim	9.73	62.37	64.54	70.04	80.13	74.46	80.43
Follitropin alfa	22.76	-	-	1.64	14.29	26.31	26.43
Infliximab	9.85	4.2	15.53	39.34	39.81	46.38	48.56
Insulin glargin	16.43	-	33.62	37.35	24.41	37.3	34.62
Pegfilgrastim	48.61	-	-	-	-	14.52	30.88
Rituximab	19.27	-	-	<1	23.93	40.81	47.06
Somatropin	9.53	87.5	84.62	100	20	0	-
Teriparatid	17.44	-	-	-	4.29	11.84	17.36
Trastuzumab	17.98	-	-	-	-	<1	6.02

Table A7 Frequency of medication switches by active substance

Category	Active substance	Proportion to all switches (%)			
		RP to RP	RP to B	B to B	B to RP
Fusion proteins	Etanercept	0.27	4.4	0.29	1.59
Hormones	Follitropin alfa	9.41	5.35	8.1	5.84
Hormones	Insulin glargin	0.27	2.95	0.17	2.72
Hormones	Somatropin	0.02	0.07	0	0
Hormones	Teriparatid	0.21	1.42	1.34	2.51
Monoclonal antibodies	Adalimumab	4.52	4.04	1.75	4.63
Monoclonal antibodies	Bevacizumab	11.38	1.67	4.31	5.98
Monoclonal antibodies	Infliximab	1.86	8.95	2.33	6.4
Monoclonal antibodies	Rituximab	21.81	11.75	31.24	13.05
Monoclonal antibodies	Trastuzumab	6.94	1.02	1.52	7.89
Low-molecular-weight heparins	Enoxaparin	25.57	0.65	0.06	30.88
Growth factors	Epoetin alfa	14.22	1.16	24.94	1.17
Growth factors	Filgrastim	2.4	50.75	21.5	8.07
Growth factors	Pegfilgrastim	1.13	5.82	2.45	9.27

Table A8 Three models (A-C) assessing determinants of biosimilar first prescription (logistic regression)

Variables	**Model A: sociodemographic variables** OR [95%CI]	**Model B: Model A + medication variables** OR [95%CI]	**Model C: Model B + provider variables** OR [95%CI]
Intercept	0.429 [0.355, 0.518]	0.831 [0.49, 1.402]	0.706 [0.399, 1.241]
Year:			
2016 (reference)			
2017	1.381 [1.129, 1.692]	1.602 [1.246, 2.062]	1.594 [1.233, 2.064]
2018	1.354 [1.113, 1.648]	1.983 [1.551, 2.539]	1.934 [1.503, 2.492]
2019	1.493 [1.246, 1.793]	2.64 [2.094, 3.332]	2.602 [2.054, 3.302]
2020	0.42 [0.356, 0.497]	2.203 [1.755, 2.769]	2.232 [1.769, 2.819]
2021	0.302 [0.256, 0.355]	3.077 [2.452, 3.867]	3.012 [2.388, 3.806]
Sex:			
Female (reference)			
Male	0.998 [0.922, 1.081]	1.137 [1.02, 1.267]	1.132 [1.014, 1.263]

Age:			
<50 (reference)			
50-64	1.302 [1.169, 1.452]	1.005 [0.867, 1.164]	1.022 [0.881, 1.185]
65-74	1.571 [1.401, 1.761]	1.044 [0.889, 1.227]	1.044 [0.887, 1.228]
>74	0.961 [0.849, 1.086]	0.825 [0.694, 0.98]	0.864 [0.725, 1.03]
Language region			
German (reference)			
French	0.578 [0.521, 0.64]	0.582 [0.51, 0.664]	0.611 [0.532, 0.7]
Italian	0.467 [0.397, 0.546]	0.744 [0.601. 0.918]	0.761 [0.612, 0.942]
Number of comorbidity:			
0 (reference)			
1	1.054 [0.932, 1.191]	0.934 [0.796, 1.094]	0.95 [0.81, 1.115]
2	1.095 [0.963, 1.244]	1.041 [0.88, 1.23]	1.05 [0.886, 1.243]
>2	0.938 [0.837, 1.051]	1.05 [0.904, 1.22]	1.08 [0.928, 1.256]
Deductible:			
Low (reference)			
High	1.067 [0.954, 1.192]	1.005 [0.868, 1.163]	0.998 [0.861, 1.155]
Managed care	1.029 [0.949, 1.116]	1.103 [0.992, 1.226]	1.095 [0.984, 1.22]
Category:			
Fusion proteins (reference)			
Hormones		1.297 [0.816, 2.081]	1.281 [0.803, 2.06]
Monoclonal antibodies		0.152 [0.116, 0.199]	0.115 [0.087, 0.152]
Low-molecular-weight heparins		0.001 [0.001, 0.001]	0.001 [0, 0.001]
Growth factors		0.235 [0.168, 0.327]	0.158 [0.112, 0.222]
Multiple package size		4.551 [3.808, 5.461]	4.64 [3.876, 5.575]
Cost per package of reference product (in CHF)			
<100			
100-599		0.254 [0.185, 0.349]	0.202 [0.145, 0.28]
>600		0.853 [0.592, 1.236]	0.657 [0.453, 0.957]
Relative price difference (%)			
<10			
10-19		0.091 [0.072, 0.115]	0.076 [0.059, 0.096]
>20		0.067 [0.053, 0.084]	0.067 [0.054, 0.084]
Number of available imitator drug:			
1 (reference)			
2		2.15 [1.671, 2.785]	2.363 [1.819, 3.093]
>2		8.143 [6.502, 10.248]	9.649 [7.614, 12.303]
Suppl			
General practicioner (reference)			
Outpatient hospital			2.477 [1.887, 3.28]
Specialist			1.417 [1.075, 1.884]
Traditional pharmacy			1.207 [0.911, 1.611]
Rest			0.998 [0.609, 1.606]
Observations	18'953	18'953	18'953
AIC	16'588	9'868	9'735
BIC	16'722	10'088	9'986

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4,5

Objectives	#3	State specific objectives, including any prespecified hypotheses		4,5
Methods				
Study design	#4	Present key elements of study design early in the paper		5,6,7
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		5,6,7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.		5,6
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	n/a. The resent study does not contain matched studies	
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable		5,6,7
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.		3,4

Bias	#9	Describe any efforts to address potential sources of bias	6,7
Study size	#10	Explain how the study size was arrived at	5,6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	5,6,7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	7,8
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	7,8
Statistical methods	#12c	Explain how missing data were addressed	8
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	8
Statistical methods	#12e	Describe any sensitivity analyses	n/a
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give	8

		information separately for exposed and unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	8
Participants	#13c	Consider use of a flow diagram	n/a, addressed in text at page 4
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	8,9
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	n/a. We excluded missing data before descriptively analysing the study population
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	8,9,10,11
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	8,9,10,11
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make	8,9,10,11

		clear which confounders were adjusted for and why they were included	
Main results	#16b	Report category boundaries when continuous variables were categorized	8,9,10,11
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	#18	Summarise key results with reference to study objectives	13
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	17
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	13,14,15,16
Generalisability	#21	Discuss the generalisability (external validity) of the study results	17

Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

Notes:

- 6b: n/a. The resent study does not contain matched studies
- 13c: n/a, addressed in text at page 4
- 14b: n/a. We excluded missing data before descriptively analysing the study population
- 20: 13,14,15,16 The STROBE checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 06.10.2023 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai