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# 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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10 1 **Initial prescriptions and medication switches of biological products: an analysis of**  
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12 2 **prescription pathways and determinants in the Swiss healthcare setting**  
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17 3 Kevin Wirth<sup>1,2\*</sup>, Stefan Boes<sup>2</sup>, Markus Näpflin<sup>1</sup>, Carola A. Huber<sup>1,3</sup>, Eva Blozik<sup>3</sup>  
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24 4 <sup>1</sup> Department of Health Sciences, Helsana Group, Zurich, Switzerland  
25

26 5 <sup>2</sup> Department of Health Sciences and Medicine, University of Lucerne, Lucerne, Switzerland  
27

28 6 <sup>3</sup> Institute of Primary Care, University of Zurich, Zurich, Switzerland  
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30  
31  
32  
33

34 7 \* Corresponding author  
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36 8 Kevin Wirth, Südstrasse 29, 8180 Bülach, [kevin.wirth.migliazza@gmail.com](mailto:kevin.wirth.migliazza@gmail.com)  
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3 10 **ABSTRACT**

4 11 **Objectives** Biological products have contributed to extraordinary advances in disease  
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7 12 treatments over the last decade. However, the cost-saving potential of imitator products, so-  
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9 13 called biosimilars, is still underresearched in Switzerland. This study aims to assess biosimilars'  
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11 14 prescriptions at treatment initiation and their determinants, as well as biological therapy  
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13 15 switches.

16 16 **Design** We analyzed longitudinal data for biosimilar prescriptions in Switzerland using  
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18 17 descriptive statistics and logistic regression to quantify the associations with individual,  
19  
20 18 pharmaceutical, and provider-related variables.

21 19 **Setting** The analysis is based on de-identified claims data of patients with mandatory health  
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23 20 insurance at Helsana, a leading Swiss health insurance.

24  
25 21 **Participants** Overall, 17'654 patients receiving at least one biological product between 2016  
26  
27 22 and 2021 were identified.

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29 23 **Primary and secondary outcome measures:** We differentiated between initial prescriptions  
30  
31 24 and follow-up prescriptions. Our regression focused on initial prescriptions due to evidence  
32  
33 25 indicating that patients tend to follow the medication prescribed at therapy initiation.

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35 26 **Results** Although biosimilars market share was low (28.6%), the number of prescriptions has  
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37 27 increased. Few medication switches were detected. Increased relative price difference was  
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39 28 associated with decreased probability of biosimilar prescriptions, whereas male sex, an increase  
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41 29 of available imitator drugs on the market and, larger packaging sizes, and prescriptions from  
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43 30 specialists or physicians in outpatient settings were associated with increased biosimilars use.

44  
45 31 **Conclusion** The low number of biosimilar prescriptions despite the proliferating biosimilar  
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47 32 market indicates a high potential for biosimilar diffusion. Our research highlights the need for  
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49 33 awareness initiatives to improve understanding among patients and physicians, enabling  
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51 34 informed, shared decision-making about biosimilar prescriptions.

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59 35 [249 of max 250 words]

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5 36 **Key words:** biosimilars, biologics, reference products, switches, initial prescription  
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## 10 **ARTICLE SUMMARY**

### 11 12 37 **Strengths and limitations of this study:**

- 13  
14 38 • First scientific study to evaluate the prescription of biosimilars using a comprehensive  
15  
16 39 set of sociodemographic, pharmaceutical, and healthcare provider variables  
17  
18 40 representing a nearly representative database in Switzerland.
- 21 41 • This research paper is the first to divide the medication treatment pathway into initial  
22  
23 42 and follow-up prescriptions, with a specific focus on the initial prescriptions. This is  
24  
25 43 particularly relevant, as initial prescriptions often influence subsequent prescribing  
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27 44 decisions as patients are less willing to switch biological medication therapy.
- 30 45 • This study was the first to assess determinants of initial prescriptions in the context of  
31  
32 46 biosimilars.
- 33 47 • Some demand-related factors (patients' health status, beliefs, and experiences) and  
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35 48 supply-related factors (physicians' incentives and beliefs) about biosimilars could not  
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37 49 be accounted using the claims data.

## 40 41 42 43 44 50 **BACKGROUND**

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47 51 Biological products increased the spectrum of available treatment options considerably in the  
48  
49 52 treatment of many cancers and autoimmune diseases. However, these medications are more  
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51 53 expensive compared to many conventional synthetic drugs as they are produced by living cells  
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53 54 and, thus, require a more complex manufacturing process. Currently, there are a considerable  
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55 55 number of biologics in the final stages of development and approval [1, 2]. The healthcare  
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57 56 systems are likely to incur substantial costs even if just a small proportion of these biologics is

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3 57 granted market approval. One lever to curb rising drug costs is the replacement of biologics  
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5 58 after patent expiration with less expensive imitator products, also known as biosimilars. Due to  
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7 59 the biotechnological manufacturing process, exact copies of the biological products are not  
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9 60 achievable. As a result, minor structural deviations in the biosimilar are unavoidable [3, 4], and  
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11 61 regulatory authorities accept them for market approval [5, 6].  
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14 62 In Switzerland, a Swiss report has estimated a cost saving potential of over 60 million Swiss  
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16 63 francs for the complete replacement of reference products with biosimilars in 2019 [7]. In the  
17  
18 64 coming years, cost saving potential will increase as several top-selling biologics will lose their  
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20 65 patent protection in Switzerland [7, 8] and corresponding biosimilars have already been  
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22 66 approved in the European Union (EU) [2, 9, 10]. However, the realization of the cost saving  
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24 67 potential us is assumed to be curbed because of skepticism about biosimilars from both the  
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26 68 patient and physician side [11–14]. At the same time, patients and their health care providers  
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28 69 seem to be less willing to switch biological products when therapy has already been started  
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30 70 [15]. Consequently, the choice of initial prescription (IP) at therapy initiation is the decisive  
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32 71 factor for following medication prescriptions. Despite the significant role of IP in shaping  
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34 72 subsequent treatment pathways, research on the prescription behavior of biological products at  
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36 73 therapy initiation and the impact of IP is limited. Existing studies have only demonstrated that  
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38 74 patients tend to remain on their initial biological treatment product once medication treatment  
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40 75 has been initiated. Thus, there is a need for further investigation into the influencing factors of  
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42 76 IP and their influence on the choice of medication path. Thus, this study aims to assess  
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44 77 biosimilars' prescriptions at treatment initiation and their determinants, as well as biological  
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46 78 therapy switches.  
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## 79 **METHODS**

### 80 **Study design and study population**

81 We analyzed administrative claims data from adult patients ( $\geq 18$  years) enrolled in mandatory  
82 health insurance at Helsana Group, a leading health insurance provider in Switzerland, and who  
83 had at least one biological product claim between 2016 and 2021 (Table A1). The Helsana  
84 database covers 15% of the Swiss population (1.2 million Swiss residents). Previous studies  
85 have shown that this database can be considered fairly representative of the Swiss general  
86 population, as the results showed only minor discrepancies between raw and adjusted results  
87 [16, 17].

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

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



### 103 **Measures**

104 The study included all patients who had at least one biosimilar available on the market at the  
105 time of IP of a biologic product. IP were defined for each patient as claims that were not  
106 preceded by other prescriptions in the same medication category within the previous 24 months.  
107 The following prescriptions were labeled as “follow-up prescriptions” (FP). We considered all  
108 claims of biological products within 12 months after IP. By restricting the follow-up period to  
109 12 months, we were able to focus on the medications that were prescribed as a result of the  
110 initial prescription rather than medications that were prescribed for unrelated reasons. This  
111 approach allowed us to evaluate the impact of the initial prescription more accurately on  
112 subsequent medication use, and to draw meaningful conclusions about prescribing patterns over  
113 time. We selected 117 biological products approved by Swissmedic from a list (Table A1)  
114 derived from the Swiss Drug Compendium that details all unique reference products and the  
115 corresponding imitator medications (based on matching, unique combinations of active  
116 ingredient, dose, and package size). We considered patient characteristics as covariates. They  
117 included sex, age group (<50, 50-64, 65-74, >74) and language region (German, French,  
118 Italian). Furthermore, information on comorbidity was assessed using the number of  
119 Pharmaceutical Cost Groups (PCG) per patient (0,1,2,>2). This metric serves as a proxy for the  
120 presence of chronic disease [18]. The Swiss healthcare system offers different cost-sharing  
121 options to patients, including low (CHF 500, 1'000) or high deductibles (i.e., CHF 1'500, 2'000,  
122 or 2'500), and integrated care models, which aim to improve patient outcomes and reduce  
123 healthcare costs by coordinating care across different healthcare providers and settings. In  
124 Switzerland, patients who participate in integrated care models receive a premium rebate in  
125 exchange for limited healthcare provider options. Thus, having a low (CHF 500, 1'000) or high  
126 deductible (i.e., CHF 1'500, 2'000, or 2'500 vs. CHF 300), and being enrolled in a managed  
127 care model were used in the analysis. A comprehensive set of variables characterized the

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3 128 prescribed medications: Prescriptions were described by category (fusion proteins, hormones,  
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5 129 monoclonal antibodies, low-molecular-weight [LMW] heparins and growth factors), whether  
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7 130 there were multiple packaging sizes, the cost per package of the reference product (in CHF,  
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9 131 100, 100-599, >600) and the relative price difference of the reference product to the  
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11 132 corresponding biosimilar (10, 10-19, >20). We also assessed the number of available imitator  
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13 133 drugs (1, 2, >2) on the market at the date of prescription. The analysis adds the aspect of  
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15 134 healthcare provider by including information on the supply channel (general practitioner,  
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17 135 outpatient hospital, specialist, traditional pharmacy).  
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21 136 Since biological products are the focus of our analysis and they include various subgroups, it  
22  
23 137 seems appropriate to address the wording of these medications to ensure consistent  
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25 138 terminology: Throughout the manuscript, we refer to the totality of all biologically  
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27 139 manufactured drugs by using the term "biological products", while the originator drugs are  
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29 140 referred to as "biologics" or as "reference products". "Biosimilars" are the imitator drugs of  
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31 141 reference products.  
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## 37 142 **Statistical analysis**

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40 143 All research participants' baseline characteristics are shown as counts and percentages, or as  
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42 144 mean and standard deviation for continuous variables. We compared patient characteristics for  
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44 145 all individuals with and without biosimilar IP. For bivariate comparisons between patients with  
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46 146 and without biosimilar IP, Fisher exact and Chi-Square tests were used accordingly. Statistical  
47  
48 147 significance was defined as a two-sided p-value of 0.05. We determined the biosimilar  
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50 148 prevalence by distinguishing between IP and FP and the prevalence of biological therapy  
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52 149 switches (number of prescriptions and patients) for each year (2016-2021). Chi-squared tests  
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54 150 were used to determine whether the prevalence was equivalent across the years. To assess the  
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56 151 determinants of biosimilar prescriptions, we used logistic regression models in which the  
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3 152 dependent variable was whether a biosimilar was prescribed as IP (0 or 1). Three different  
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5 153 logistic models with different sets of variables were computed (Table A8). Both, Model B and  
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8 154 C, show similar results and a better fit of the estimates compared to Model A based on the  
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10 155 goodness-of-fit criteria (AIC, BIC). For the manuscript, we proceed with Model C because we  
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12 156 are mainly interested in the associations with biosimilar prescriptions from all three points of  
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15 157 view (patient, medication, physician). Odds ratios (OR) and corresponding 95% confidence  
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17 158 intervals (CI) were calculated for each regression coefficient. The success rate in the binomial  
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19 159 model was denoted by the term "occurrence" to improve the results' readability. All analyses  
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21 160 were performed using R version 4.2.1.

## 26 161 RESULTS

29 162 The study sample consisted of 18'953 patients with at least one prescription of biological  
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31 163 products. Patient characteristics of the study population at the time of IP, stratified by type of  
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33 164 IP (reference product 81.5%, biosimilar 18.5%), are presented in Table 1. Female patients more  
34  
35 165 frequently received biosimilars than males (60.6%). The mean age was slightly higher in men  
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37 166 (61.7 years) compared to women (59.0 years). LMW heparins were the most prescribed  
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39 167 reference products (54.2%), with growth hormones constituting the largest group of biosimilars  
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41 168 (57.9%).

46 **Table 1. Comparison of patient characteristics at IP between patients with reference**  
47 **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%)	

<sup>1</sup>) Fisher exact test, <sup>2</sup>) Chi-Square test

Signif. codes: '\*\*\*' 0.001

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

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

174 Table 2 describes the overall frequency of biologicals products over the observation period  
 175 including the absolute and relative frequency of biosimilars in comparison to all biological  
 176 prescriptions. Of all biological products (IP and FP), 28.6% were biosimilar prescriptions. In  
 177 absolute values, the prescription rate of biosimilars increased over time (from 1'016 in 2016 to  
 178 6'976 in 2021). However, there is no discernible trend in the relative share of biosimilars in all  
 179 prescriptions of biological products (35.5% in 2016, 39.2% in 2017, 45.2% in 2018, 41.6% in  
 180 2019, 26.3% in 2020 and 22.5% in 2021). Furthermore, the share of biosimilars in FPs was  
 181 higher than in IPs in every year. The growth factor Filgrastim was the most frequently prescribed  
 182 active substance of biosimilars in IPs and FPs (53.1% and 36.2% respectively), while  
 183 enoxaparin was the most frequently prescribed active substance of reference products in IPs  
 184 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

Chi-Square test, Signif. codes: '\*\*\*' <0.001

185 Of the study population, only a small subset (n=1'492, 8.5%) experienced at least one  
 186 medication switch (Table 3). Most patients had switches between reference products (n=867,  
 187 58.1%), followed by switches from reference product to biosimilar (n=331, 22.2%), from  
 188 biosimilar to reference product (n=297, 19.9%) and switches between biosimilars (n=286,

189 19.2%). The number of patients with at least one switch increased between 2016 and 2021  
 190 (from 28 to 662), whereby the numbers of patients with switches between reference products  
 191 increased most prominently (from 25.0% in 2016 to 62.1% in 2021). Switches between  
 192 reference products and between biosimilars occurred most often for Enoxaparin and Rituximab,  
 193 respectively (Table A7). The most common switches from reference product to biosimilar and  
 194 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

Chi-Square test  
 Signif. codes: '\*\*\*' <0.001

195 As far as the regression results are concerned, the odds of prescribing biosimilars at IP have  
 196 been increasing over the years (Fig.1, Table A8). Male sex was associated with 13.2% higher  
 197 odds of receiving biosimilar IP, whereas residence in a French or Italian-speaking region had a  
 198 38.9% and 23.9%, respectively, lower occurrence of a biosimilar IP. None of the insurance-  
 199 related variables showed a significant association with biosimilars IPs. In terms of  
 200 pharmaceutical variables, monoclonal antibodies, LMW heparins and growth factors were  
 201 associated with substantially lower biosimilar IP occurrences (-88.5%, -99.9% and -84.2%)  
 202 than fusion proteins. The availability of multiple packaging sizes was associated with 4.6-fold  
 203 higher odds of biosimilar IP compared to medications with solely one packaging size. For the  
 204 absolute package price, no consistent pattern was observed, as medications with prices between

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3 205 100 and 599 francs per pack decreased the odds by 79.8% compared to the baseline (<100  
4  
5 206 CHF), whereas the odds in the highest prize category (>600 CHF) were lower by 34.3%.  
6  
7 207 However, compared to products with a <10% price difference between reference product and  
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9 208 biosimilar, higher price reductions were associated with decreased occurrence of biosimilar IP:  
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11 209 medications with 10-19% price difference had 92.4% lower odds and medications with more  
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13 210 than 20% had even 93.3% lower odds. On the contrary, increasing the number of available  
14  
15 211 imitator medications of prescription (2 and >2) had substantially higher (2.36-fold and 9.65-  
16  
17 212 fold) odds of biosimilar IP compared to prescriptions with only one available biosimilar. As far  
18  
19 213 as provider variables are concerned, physicians in the outpatient hospital setting prescribed far  
20  
21 214 more biosimilars compared to general practitioners (2.48-fold higher odds). The occurrence of  
22  
23 215 biosimilar IP was also 41.7% higher in patients who had been prescribed biological products  
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25 216 by a specialist than in patients who had received the equivalent medications from a general  
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27 217 practitioner.  
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## 35 218 **DISCUSSION**

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38 219 The growing market for biosimilars can explain the observed increase in the number of  
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40 220 biosimilar prescriptions over time: from 15 approved biosimilars in 2016 the market for  
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42 221 biosimilars has grown (15 in 2017; 22 in 2018; 42 in 2019; 70 in 2020) up to 78 biosimilars in  
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44 222 2021 (Table A1) [7, 19]. A longer time on the market gives the biosimilar a better chance to  
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46 223 establish itself and gain market share. Despite the increase, the biosimilars quota remained  
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48 224 relatively low. In the literature, this low share in Switzerland has already been documented: in  
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50 225 2019, market sales of all biological products with available biosimilars totaled CHF 449 million  
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52 226 in 2019, of which biosimilars accounted for only CHF 42 million (9.4%) [7]. Furthermore,  
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54 227 market share of biosimilars seems to be low compared to other countries. For example,  
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56 228 biosimilars account for 80% of the biological product market in Norway [20]. In Germany, two  
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3 229 studies reported an average biosimilar ratio between 40.5% and 51.9% in 2019 [21, 22]. In the  
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5 230 present study we observed substantially lower average biosimilar quota of 28.0%. Infiximab is  
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7 231 a particularly compelling example, with the biosimilar share reaching 26% in Germany after  
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9 232 only 12 months on the market (2017) and rising to 64-68% of the biosimilar market in 2019.  
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11 233 By contrast, infiximab achieved a market share of only 22% in Switzerland in 2019 [7]. The  
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13 234 low market share of biosimilars in Switzerland may be due to various reasons: Studies have  
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15 235 shown that knowledge deficits among physicians and among patients may lead to reluctance  
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17 236 regarding the use of biosimilars [11–14]. According to survey studies [23–27], between 15-  
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19 237 30% of the population is thought to have a negative perception of these imitator drugs. This  
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21 238 distrust may be driven by a perceived weakness in the evidence base concerning efficacy and  
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23 239 safety of biosimilars, as only bioequivalence needs to be demonstrated for biosimilar approval.  
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25 240 However, there is increasing evidence of equivalent safety and efficacy of biosimilars, along  
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27 241 with evidence of bioequivalence [28–30]. Furthermore, a challenge for newly approved  
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29 242 biosimilars is the difficulty in extending conclusions from RCTs to the broader population that  
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31 243 will use the biosimilar. This is because RCTs typically enroll a more homogeneous population,  
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33 244 and certain patient groups, such as pediatric, elderly, and comorbid populations, as well as  
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35 245 patients with polypharmacy, are often underrepresented in these trials [31–33]. As a result,  
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37 246 prescribers may be skeptical about the use of biosimilars in these patient populations because  
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39 247 of the lack of data. Moreover, the current incentive system discourages the prescription of  
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41 248 biosimilars for self-dispensing doctors and pharmacies as they are rewarded for prescribing the  
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43 249 more expensive product by a bigger profit margin [7]. On the other side, under a capitation  
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45 250 payment model, managed care physicians may have a financial incentive to prescribe lower-  
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47 251 cost biosimilars in order to maximize profits. However, if physicians are not properly educated  
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49 252 about the safety and efficacy of biosimilars, they may be hesitant to prescribe them.  
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3 253 That only a small subset (n=1'492, 8.5%) experienced at least one medication switch can be  
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5 254 explained by the reluctance of patients to switch to a biosimilar medication due to the fear of  
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7 255 experiencing new and unknown side effects. Patients who have been using a particular  
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9 256 medication for a long time and have become accustomed to its efficacy and safety profile may  
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11 257 be hesitant to switch to a biosimilar, which they perceive as being different and possibly  
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13 258 inferior. Nevertheless, efficacy of biosimilar switching has been observed [7, 28–30, 34, 35].  
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15 259 According to a systematic literature review based on 90 published studies, the great majority of  
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17 260 the publications did not report differences in immunogenicity, safety, or efficacy when patients  
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19 261 switched to biosimilars. Three large studies did not show differences in efficacy or safety after  
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21 262 multiple switches between reference product and biosimilar [36–38]. Only two publications  
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23 263 reported a loss of efficacy or increased dropout rates [39, 40]. Often, this very knowledge and  
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25 264 awareness about the safety and efficacy of switching to new treatment options lack for  
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27 265 prescribing physicians who rely on solid, evidence-based data to make treatment decisions [41–  
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29 266 43].  
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31 267 The regression results revealed that biosimilar IP rates were lower in French-speaking cantons.  
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33 268 These regional variations may be caused by a variety of variables, including a higher  
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35 269 concentration of medical services in urban regions, various patient characteristics, and cultural  
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37 270 variations between cantons [44, 45]. The strongest barrier for biosimilar prescriptions was the  
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39 271 increasing relative price difference between biosimilar and reference product. A possible  
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41 272 explanation is that healthcare providers may have less experience with biosimilars with a higher  
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43 273 price difference or may perceive them as less established and less proven than biosimilars with  
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45 274 a lower price difference. This lack of familiarity or perceived risk may contribute to reluctance  
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47 275 in prescribing biosimilars with a higher price difference. It is also important to consider the role  
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49 276 of financial incentives and reimbursement policies in biosimilar prescribing: Currently,  
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51 277 dispensation channels receive a larger profit margin when distributing the more expensive  
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3 278 reference product under the present price-dependent margin [19]. This incentive system seems  
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5 279 to be characteristic for Switzerland, as studies conducted in European countries did not find a  
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7 280 relationship between price difference and biosimilar dissemination [46–48]. This might be  
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9 281 attributed to several factors that differentiate Switzerland from other European countries:  
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11 282 Cantonal differences in self-dispensing regulation, the country's different prescribing cultures  
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13 283 and guidelines across its language regions, and capitation is implemented only in relatively few  
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15 284 cases in Switzerland. In our analysis, male patients had more biosimilar IP. According to  
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17 285 studies, women were often more skeptical of imitator drugs [23, 49–52] and they more  
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19 286 frequently believe that they are more responsive to medications than men [53–55]. This can  
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21 287 have an impact on their confidence in biosimilars, making female patients more aware of  
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23 288 potential side effects or lack thereof. Biosimilar IPs were prescribed more frequently for fusion  
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25 289 proteins compared to other categories which indicates an increased acceptance of imitator  
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27 290 products in this drug class. This is supported by the relatively early market entry (2018) and by  
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29 291 a meta-analysis showing comparable results in terms of efficacy and safety between reference  
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31 292 product and biosimilars [56]. The strongest facilitator of biosimilar prescriptions was the  
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33 293 amount of available biosimilars, which is in line with the findings of a prior study [46, 57].  
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35 294 Thus, the replacement of reference products by biosimilars seems to be better accepted in  
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37 295 market segments with many imitator products. This finding is probably associated with the  
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39 296 larger collective promotional effort from multiple players involved in the field to favor  
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41 297 biosimilars; it is noteworthy that the largest adoption of biosimilars (Filgrastim) has been  
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43 298 partially attributable to the fact that numerous biosimilar producers have commercialized  
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45 299 different products, whereas there is only one company branding the reference product [58]. We  
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47 300 found more biosimilar IPs for specialists and outpatient hospital physicians than GP. These  
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49 301 findings are in line with existing literature that showed more biosimilars from specialists who  
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51 302 reported a higher confidence in the comparability of biosimilars than GPs [59, 60]. Differences  
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3 303 in care providers may be due to a variety of reasons: some healthcare providers may not be  
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5 304 interested in stockpiling too many different medications and additional biosimilars, as they  
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8 305 sometimes have large storage requirements (cooling, expiration date) and , thus, are associated  
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10 306 with a significant financial risk [19]. In addition, it has been demonstrated that the dissemination  
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12 307 of knowledge about new prescription options is heterogeneous because there are large learning  
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14 308 costs associated with the treatment effects of new therapy options, which rely on the training  
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16 309 and experience of the doctor [61]. Despite the fact that a previous study conducted in the context  
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18 310 of generic drugs showed that older people are less likely to use imitator products when offered  
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20 311 a choice [23, 57], we did not observe an age-dependency of biosimilar prescriptions.

23 312 The most valuable strength of this study is the extensive dataset of biosimilar prescriptions and  
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25 313 potential influencing factors including sociodemographic, pharmaceutical and healthcare  
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27 314 provider variables that were gathered from a representative sample of the Swiss population.

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29 315 The main limitation is the dearth of clinical data in our database (e.g., disease severity, clinical  
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31 316 diagnosis, and reason for biosimilar utilization). However, we attempted to mitigate this by  
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33 317 utilizing comorbidity measures based on reimbursed prescriptions to control for potential  
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35 318 confounders. Another limitation of our study is that the follow-up period for the prescriptions  
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37 319 was limited to 12 months. This time frame may have led to the exclusion of some prescriptions,  
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39 320 potentially introducing bias into our results. Nevertheless, we observed that a significant  
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41 321 number of patients (7'608, which accounts for 43.1% of the total) were given only one  
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43 322 prescription, indicating that any bias arising from this limitation is expected to be insignificant.

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45 323 The relatively low market share of biosimilars compared to other EU countries highlighted in  
46  
47 324 our research paper has important implications for the adoption and utilization of these  
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49 325 products in Switzerland. Patients and physicians should be better and objectively informed  
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51 326 about biosimilars in order to increase the acceptance [47, 48]. Also, for example, a clear and  
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53 327 conspicuous indication of the prescribed active substance on the medication package for both  
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3 328 the reference product and the imitator drug, for instance, could enhance patient confidence  
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5 329 [42]. To address the perceived uncertainty and mistrust in imitator products, the evidence base  
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7 330 should be further strengthened: direct evidence to help explain some of the practical aspects  
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9 331 related to the use of biosimilars can be provided by retrospective studies, national databases  
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11 332 and registries that track the long-term immunogenicity and safety of biosimilars [62–67]. In  
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13 333 addition, the incentive system for healthcare providers seems to be designed in such a way  
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15 334 that fewer biosimilars are prescribed. Thus, these incentives should be eliminated, for  
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17 335 example by introducing a fixed margin that always remunerates the medication supplier the  
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19 336 same regardless of the prescribed product (reference product or biosimilar). In order to exploit  
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21 337 the cost saving potential of biosimilars, the aforementioned measures should be targeted to  
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23 338 biosimilars with a noticeable price difference compared to their reference products, and that  
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25 339 still possess relatively low biosimilar market share. Taking into account the findings  
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27 340 presented in Table A6, notable examples of these biosimilars include Bevacizumab,  
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29 341 Follitropin alfa, and Pegfilgrastim.  
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33 342 However, the decision to prescribe an imitator drug should not merely be motivated by the  
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35 343 cost-saving potential but should ensure appropriate health care provision for the patients.  
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37 344 Therefore, it is crucial for healthcare providers to engage in shared-decision making with their  
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39 345 patients to determine the most appropriate treatment option based on their individual medical  
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41 346 situation.  
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## 347 **CONCLUSION**

348 Despite an increase of available biosimilars in Switzerland between 2016 and 2021, the  
349 biosimilars market share remained relatively low over time. In addition, biological therapy  
350 switches were rarely observed, highlighting the importance of IPs. Our study suggests that  
351 greater acceptance and higher utilization of biosimilars may be associated with the availability  
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3 352 of different package sizes and lower price differences between biosimilars and their reference  
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5 353 products. Patients and providers should be informed about biosimilars in a timely and  
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7 354 appropriate manner, and outdated incentive structures have to be changed to increase the use of  
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10 355 biosimilars.

11  
12 *[please insert Appendix here]*  
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27  
28 360 additional role in the study design, data collection and analysis, decision to publish, or  
29  
30 361 preparation of the manuscript.  
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35 362 **Author contributions** KW, MN and CH designed the study. MN did data preparation and data  
36  
37 363 management. MN and KW performed the statistical analyses, with the contribution of SB, CH  
38  
39 364 and EB. KW drafted the main manuscript text. All authors assisted in the interpretation of the  
40  
41 365 results and critically revised the manuscript. All authors have read and approved the manuscript.  
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47 366 **Data availability** Helsana provides the data that support up the findings of this research.  
48  
49 367 (<https://www.helsana.ch/en/helsana-group>). These data, which were used under license for the  
50  
51 368 present study and are not accessible to the general public, are subject to restrictions. But with  
52  
53 369 Helsana's consent and upon reasonable request, data are available from the authors  
54  
55 370 ([gesundheitskompetenz@helsana.ch](mailto:gesundheitskompetenz@helsana.ch)).  
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3 371 **Ethics approval** The data used in this study were retrospective, pre-existing, de-identified, and  
4  
5 372 anonymous in accordance with privacy laws and regulations. This study was free from the  
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7 373 provisions of the Swiss Federal Law on Human Research because it used retrospective, de-  
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9 374 identified, and anonymized data (Humanforschungsgesetz) [68] and was thus exempted from  
10  
11 375 receiving clearance from the regional ethics committee (the ethical committee of the Canton of  
12  
13 376 Zurich) as well as from obtaining the patients' informed consent.  
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24 378 **Consent to publish** Not applicable.  
25  
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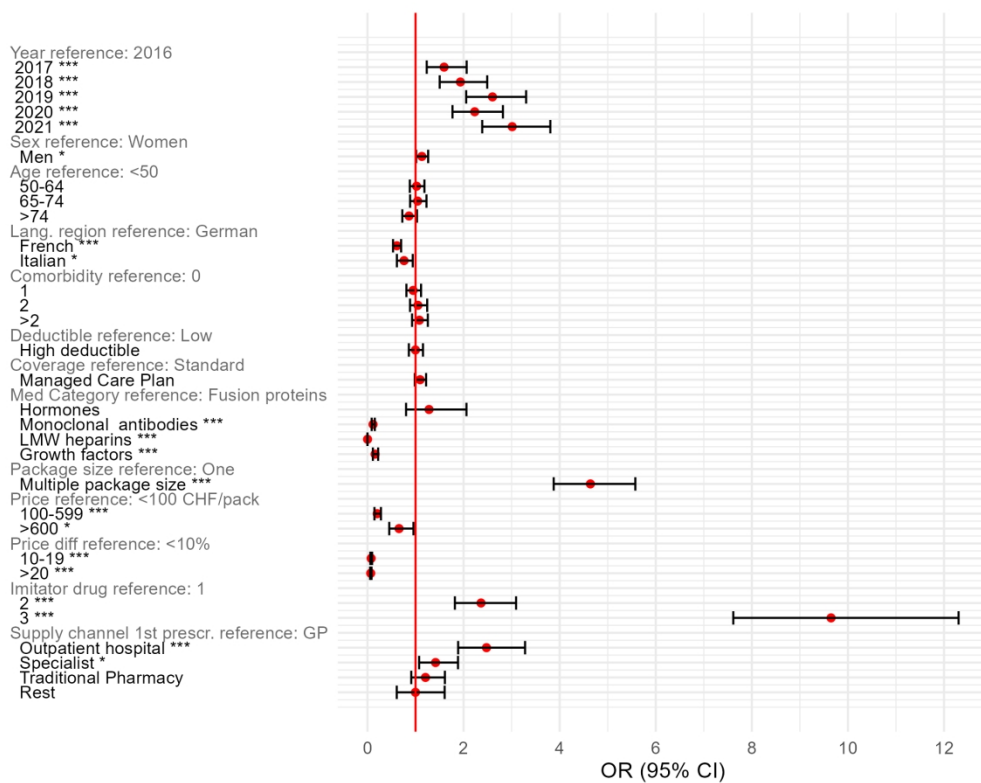
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6 598 **Figure 1 Determinants of biosimilar initial prescription (logistic regression)**  
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Table A1 Substitution catalogue: reference product & biosimilar (2016-2021)

ATC	Reference Product			Biosimilar			
	medication	Dose (mg) / unit	cost (in CHF)	medication	Reimburment date	Dose (mg) / unit	cost (in CHF)
<i>Low-molecular-weight heparins</i>							
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
<i>Growth factors</i>							
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	Epex	0.008 / 6	71.5	Binocrit	01.10.2009	0.008 / 6	66.15
B03	Epex	0.017 / 6	126.55	Binocrit	01.10.2009	0.017 / 6	115.7
B03	Epex	0.025 / 6	181.65	Binocrit	01.10.2009	0.025 / 6	165.25
B03	Epex	0.037 / 6	236.75	Binocrit	01.10.2009	0.037 / 6	214.7
B03	Epex	0.046 / 6	291.8	Binocrit	01.10.2009	0.046 / 6	264.5
B03	Epex	0.092 / 6	567.2	Binocrit	01.10.2009	0.092 / 6	512.1
<i>Hormones</i>							
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
<i>Fusion proteins</i>							
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



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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	Model B: Model A + medication variables	Model C: Model B + provider variables
	Coeff. [95%CI]	Coeff. [95%CI]	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]

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3	Age:			
4	<50 (reference)			
5	50-64	1.302 [1.169, 1.452]	1.005 [0.867, 1.164]	1.022 [0.881, 1.185]
6	65-74	1.571 [1.401, 1.761]	1.044 [0.889, 1.227]	1.044 [0.887, 1.228]
7	>74	0.961 [0.849, 1.086]	0.825 [0.694, 0.98]	0.864 [0.725, 1.03]
8	Language region			
9	German (reference)			
10	French	0.578 [0.521, 0.64]	0.582 [0.51, 0.664]	0.611 [0.532, 0.7]
11	Italian	0.467 [0.397, 0.546]	0.744 [0.601, 0.918]	0.761 [0.612, 0.942]
12	Number of comorbidity:			
13	0 (reference)			
14	1	1.054 [0.932, 1.191]	0.934 [0.796, 1.094]	0.95 [0.81, 1.115]
15	2	1.095 [0.963, 1.244]	1.041 [0.88, 1.23]	1.05 [0.886, 1.243]
16	>2	0.938 [0.837, 1.051]	1.05 [0.904, 1.22]	1.08 [0.928, 1.256]
17	Deductible:			
18	Low (reference)			
19	High	1.067 [0.954, 1.192]	1.005 [0.868, 1.163]	0.998 [0.861, 1.155]
20	Managed care	1.029 [0.949, 1.116]	1.103 [0.992, 1.226]	1.095 [0.984, 1.22]
21	Category:			
22	Fusion proteins (reference)			
23	Hormones		1.297 [0.816, 2.081]	1.281 [0.803, 2.06]
24	Monoclonal antibodies		0.152 [0.116, 0.199]	0.115 [0.087, 0.152]
25	Low-molecular-weight heparins		0.001 [0.001, 0.001]	0.001 [0, 0.001]
26	Growth factors		0.235 [0.168, 0.327]	0.158 [0.112, 0.222]
27	Multiple package size		4.551 [3.808, 5.461]	4.64 [3.876, 5.575]
28	Cost per package of reference			
29	product (in CHF)			
30	<100			
31	100-599		0.254 [0.185, 0.349]	0.202 [0.145, 0.28]
32	>600		0.853 [0.592, 1.236]	0.657 [0.453, 0.957]
33	Relative price difference (%)			
34	<10			
35	10-19		0.091 [0.072, 0.115]	0.076 [0.059, 0.096]
36	>20		0.067 [0.053, 0.084]	0.067 [0.054, 0.084]
37	Number of available imitator drug:			
38	1 (reference)			
39	2		2.15 [1.671, 2.785]	2.363 [1.819, 3.093]
40	>2		8.143 [6.502, 10.248]	9.649 [7.614, 12.303]
41	Suppl			
42	General practitioner (reference)			
43	Outpatient hospital			2.477 [1.887, 3.28]
44	Specialist			1.417 [1.075, 1.884]
45	Traditional pharmacy			1.207 [0.911, 1.611]
46	Rest			0.998 [0.609, 1.606]
47	Observations	18'953	18'953	18'953
48	AIC	16'588	9'868	9'735
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# 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
<b>Title and abstract</b>		
Title	<a href="#">#1a</a> Indicate the study's design with a commonly used term in the title or the abstract	Title page
Abstract	<a href="#">#1b</a> Provide in the abstract an informative and balanced summary of what was done and what was found	1
<b>Introduction</b>		
Background / rationale	<a href="#">#2</a> Explain the scientific background and rationale for the investigation being reported	2,3

1	Objectives	<a href="#">#3</a>	State specific objectives, including any	3
2			prespecified hypotheses	
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6	<b>Methods</b>			
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10	Study design	<a href="#">#4</a>	Present key elements of study design early in the	3,4,5
11			paper	
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15	Setting	<a href="#">#5</a>	Describe the setting, locations, and relevant	4,5,6
16			dates, including periods of recruitment, exposure,	
17			follow-up, and data collection	
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23	Eligibility criteria	<a href="#">#6a</a>	Give the eligibility criteria, and the sources and	4
24			methods of selection of participants. Describe	
25			methods of follow-up.	
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30	Eligibility criteria	<a href="#">#6b</a>	For matched studies, give matching criteria and	n/a. The resent study
31			number of exposed and unexposed	does not contain
32				matched studies
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38	Variables	<a href="#">#7</a>	Clearly define all outcomes, exposures,	4,5,6
39			predictors, potential confounders, and effect	
40			modifiers. Give diagnostic criteria, if applicable	
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46	Data sources /	<a href="#">#8</a>	For each variable of interest give sources of data	3,4
47	measurement		and details of methods of assessment	
48			(measurement). Describe comparability of	
49			assessment methods if there is more than one	
50			group. Give information separately for for	
51			exposed and unexposed groups if applicable.	
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1	Bias	<a href="#">#9</a>	Describe any efforts to address potential sources	6,7
2			of bias	
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6	Study size	<a href="#">#10</a>	Explain how the study size was arrived at	4
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9	Quantitative	<a href="#">#11</a>	Explain how quantitative variables were handled	4,5,6
10	variables		in the analyses. If applicable, describe which	
11			groupings were chosen, and why	
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16	Statistical	<a href="#">#12a</a>	Describe all statistical methods, including those	5,6
17	methods		used to control for confounding	
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20	Statistical	<a href="#">#12b</a>	Describe any methods used to examine	5,6
21	methods		subgroups and interactions	
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25	Statistical	<a href="#">#12c</a>	Explain how missing data were addressed	5,6 upon request of
26	methods			reviewer 2
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30	Statistical	<a href="#">#12d</a>	If applicable, explain how loss to follow-up was	6,7
31	methods		addressed	
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34	Statistical	<a href="#">#12e</a>	Describe any sensitivity analyses	n/a
35	methods			
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39	<b>Results</b>			
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44	Participants	<a href="#">#13a</a>	Report numbers of individuals at each stage of	3,4, upon request of
45			study—eg numbers potentially eligible, examined	reviewer 2
46			for eligibility, confirmed eligible, included in the	
47			study, completing follow-up, and analysed. Give	
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1		information separately for exposed and	
2		unexposed groups if applicable.	
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6	Participants	<a href="#">#13b</a> Give reasons for non-participation at each stage	4
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9	Participants	<a href="#">#13c</a> Consider use of a flow diagram	4
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12	Descriptive data	<a href="#">#14a</a> Give characteristics of study participants (eg	7,8
13		demographic, clinical, social) and information on	
14		exposures and potential confounders. Give	
15		information separately for exposed and	
16		unexposed groups if applicable.	
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24	Descriptive data	<a href="#">#14b</a> Indicate number of participants with missing data	n/a. We excluded
25		for each variable of interest	missing data before
26			descriptively
27			analysing the study
28			population
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36	Descriptive data	<a href="#">#14c</a> Summarise follow-up time (eg, average and total	7,8,9,10
37		amount)	
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42	Outcome data	<a href="#">#15</a> Report numbers of outcome events or summary	7,8,9,10
43		measures over time. Give information separately	
44		for exposed and unexposed groups if applicable.	
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49	Main results	<a href="#">#16a</a> Give unadjusted estimates and, if applicable,	7,8,9,10,11
50		confounder-adjusted estimates and their	
51		precision (eg, 95% confidence interval). Make	
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1		clear which confounders were adjusted for and	
2		why they were included	
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6	Main results	<a href="#">#16b</a> Report category boundaries when continuous	7,8,9,10,11
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8		variables were categorized	
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11	Main results	<a href="#">#16c</a> If relevant, consider translating estimates of	11
12		relative risk into absolute risk for a meaningful	
13		time period	
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18	Other analyses	<a href="#">#17</a> Report other analyses done—eg analyses of	n/a
19		subgroups and interactions, and sensitivity	
20		analyses	
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26	<b>Discussion</b>		
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29	Key results	<a href="#">#18</a> Summarise key results with reference to study	12
30		objectives	
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35	Limitations	<a href="#">#19</a> Discuss limitations of the study, taking into	16
36		account sources of potential bias or imprecision.	
37		Discuss both direction and magnitude of any	
38		potential bias.	
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45	Interpretation	<a href="#">#20</a> Give a cautious overall interpretation considering	12,13,14,15
46		objectives, limitations, multiplicity of analyses,	
47		results from similar studies, and other relevant	
48		evidence.	
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54	Generalisability	<a href="#">#21</a> Discuss the generalisability (external validity) of	15,16
55		the study results	
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1 Other

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3 Information

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6 Funding #22 Give the source of funding and the role of the 17  
7 funders for the present study and, if applicable,  
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9 for the original study on which the present article  
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16 Notes:

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20 • 6b: n/a. The present study does not contain matched studies  
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23 • 14b: n/a. We excluded missing data before descriptively analysing the study population  
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26 • 20: 14,15,16,17 The STROBE checklist is distributed under the terms of the Creative Commons  
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# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2023-077454.R1
Article Type:	Original research
Date Submitted by the Author:	09-Oct-2023
Complete List of Authors:	Wirth, Kevin; Helsana Versicherungen AG, Boes, Stefan; University of Lucerne, Department of Health Sciences and Medicine Näpflin, Markus; Helsana Group, Department of Health Sciences Huber, Carola; Helsana Health Insurance Co, ; University Hospital Zurich, Blozik, Eva; University of Zurich, Institute of Primary Care
<b>Primary Subject Heading</b>:	Health services research
Secondary Subject Heading:	Health policy, Medical management
Keywords:	PUBLIC HEALTH, Health Literacy, MEDICAL EDUCATION & TRAINING

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3 1 **Initial prescriptions and medication switches of biological products: an analysis of**  
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5 2 **prescription pathways and determinants in the Swiss healthcare setting**  
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10 3 Kevin Wirth<sup>1,2\*</sup>, Stefan Boes<sup>2</sup>, Markus Näpflin<sup>1</sup>, Carola A. Huber<sup>1,3</sup>, Eva Blozik<sup>3</sup>  
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14 4 <sup>1</sup> Department of Health Sciences, Helsana Group, Zurich, Switzerland  
15

16 5 <sup>2</sup> Department of Health Sciences and Medicine, University of Lucerne, Lucerne, Switzerland  
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18 6 <sup>3</sup> Institute of Primary Care, University of Zurich, Zurich, Switzerland  
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22 7 \*Correspondence to:  
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24 8 Kevin Wirth, Südstrasse 29, 8180 Bülach, Switzerland  
25

26 9 [kevin.wirth.migliazza@gmail.com](mailto:kevin.wirth.migliazza@gmail.com)  
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36 11 **ABSTRACT**

37 12 **Objectives** Biological products have contributed to extraordinary advances in disease  
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39 13 treatments over the last decade. However, the cost-saving potential of imitator products, so-  
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41 14 called biosimilars, is still under-researched in Switzerland. This study aims to assess  
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43 15 biosimilars' prescriptions at treatment initiation and their determinants, as well as biological  
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45 16 therapy switches.  
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49 17 **Design** The study included all patients who had at least one biosimilar available on the market  
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51 18 at the time when they were prescribed a biologic product. We analyzed longitudinal data for  
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53 19 biosimilar prescriptions in Switzerland using descriptive statistics and logistic regression to  
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55 20 quantify the associations with individual, pharmaceutical, and provider-related variables.  
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3 21 **Setting** The analysis is based on de-identified claims data of patients with mandatory health  
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5 22 insurance at Helsana, one of the Swiss health insurances with a substantial enrollee base in  
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7 23 mandatory health insurance.

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10 24 **Participants** Overall, 18,953 patients receiving at least one biological product between 2016  
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12 25 and 2021 were identified.

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14 26 **Outcome measures:** We differentiated between initial prescriptions and follow-up  
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16 27 prescriptions. Our regression focused on initial prescriptions due to evidence indicating that  
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18 28 patients tend to follow the medication prescribed at therapy initiation.

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20 29 **Results** Although biosimilars market share was low (28.6%), the number of prescriptions has  
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22 30 increased (from 1016 in 2016 to 6976 in 2021). Few patients with medication switches (n=1492,  
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24 31 8.5%) were detected. Increased relative price difference (difference in the price of available  
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26 32 biosimilars relative to price of corresponding reference product) was associated with decreased  
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28 33 probability of biosimilar prescriptions, whereas male sex, an increase of available imitator  
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30 34 drugs on the market and, larger packaging sizes, and prescriptions from specialists or physicians  
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32 35 in outpatient settings were associated with increased biosimilars use.

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34 36 **Conclusion** The low number of biosimilar prescriptions despite the proliferating biosimilar  
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36 37 market indicates a high potential for biosimilar diffusion. The findings indicate that patients  
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38 38 typically adhere to the therapy options initially chosen and are less inclined to make changes  
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40 39 following the initiation of treatment. Our research highlights the need for awareness initiatives  
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42 40 to improve understanding among patients and physicians, enabling informed, shared decision-  
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44 41 making about biosimilar prescriptions.

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47 42 **Keywords:** biosimilars, biologics, reference products, switches, initial prescription  
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### 43 **Strengths and limitations of this study**

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

### 53 **INTRODUCTION**

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

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

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3 67 reductions correlating with the adoption rate of biosimilars [7]. In Switzerland, a Swiss report  
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5 68 has estimated a cost saving potential of over 60 million Swiss francs for the complete  
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7 69 replacement of reference products with biosimilars in 2019 [8]. In the coming years, cost saving  
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10 70 potential will increase as several top-selling biologics will lose their patent protection in  
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12 71 Switzerland [8, 9] and corresponding biosimilars have already been approved in the European  
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14 72 Union (EU) [2, 10, 11]. However, the realization of the cost saving potential us is assumed to  
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17 73 be curbed because of skepticism about biosimilars from both the patient and physician side [12–  
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19 74 15]. At the same time, patients and their health care providers seem to be less willing to switch  
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22 75 biological products when therapy has already been started [16–20]. Consequently, the choice  
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24 76 of initial prescription (IP) at therapy initiation is the decisive factor for following medication  
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26 77 prescriptions. Despite the significant role of IP in shaping subsequent treatment pathways,  
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28 78 research on the prescription behavior of biological products at therapy initiation and the impact  
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31 79 of IP is limited. Existing studies have only demonstrated that patients tend to remain on their  
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33 80 initial biological treatment product once medication treatment has been initiated [21]. Thus,  
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35 81 there is a need for further investigation into the influencing factors of IP and their influence on  
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37 82 the choice of medication path. Thus, this study aims to assess biosimilars' prescriptions at  
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40 83 treatment initiation and their determinants, as well as biological therapy switches.

## 44 84 **METHODS**

### 48 85 **Study design and population**

51 86 We studied adult patients ( $\geq 18$  years) with at least one biological product claim between 2016  
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53 87 and 2021, insured by Helsana Group, a major Swiss health insurer. (Table A1 in supplementary  
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55 88 file). The Helsana database covers 15% of Switzerland's population (1.2 million residents) and  
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3 89 is regarded as representative, as prior research found minor differences between raw and  
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5 90 adjusted results [22, 23].  
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8 91 In Switzerland, medication reimbursement is governed by the Federal Law on Health Insurance,  
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10 92 which mandates that basic health insurance must cover the costs of essential medications.  
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12 93 Swissmedic regulates the market entry of medications, while the Federal Office of Public  
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14 94 Health oversees the establishment of the reimbursement list, which determines the extent to  
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16 95 which a medication is reimbursed. Switzerland's medication reimbursement system aims to  
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18 96 balance access to essential medications with cost control: To be eligible for reimbursement,  
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20 97 medications must demonstrate efficacy, safety, and cost-effectiveness compared to standard  
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22 98 treatments. As such, all of the biological products included in this study are presumed to have  
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24 99 fulfilled these requirements.  
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## 30 100 **Measures**

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33 101 The study included all patients who had at least one biosimilar available on the market at the  
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35 102 time of IP of a biologic product. This enabled us to explore the determinants of non-prescription  
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37 103 of biosimilars despite their availability. IP were defined for each patient as claims that were not  
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39 104 preceded by other prescriptions in the same medication category within the previous 24 months.  
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41 105 Prescriptions that followed within 12 months were labeled as “follow-up prescriptions” (FP).  
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43 106 By restricting the follow-up period to 12 months, we were able to focus on the medications that  
44  
45 107 were prescribed as a result of the initial prescription rather than medications that were  
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47 108 prescribed for unrelated reasons. This approach allowed us to evaluate the impact of the initial  
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49 109 prescription more accurately on subsequent medication use. We selected 117 biological  
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51 110 products approved by Swissmedic from a list (Table A1 in supplementary file) derived from  
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53 111 the Swiss Drug Compendium.  
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3 112 We considered patient characteristics as covariates, including sex, age group (<50, 50-64, 65-  
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5 113 74, >74) and language region (German, French, Italian). We assessed comorbidity using the  
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7 114 number of Pharmaceutical Cost Groups (PCG) per patient (0,1,2,>2). PCGs are a recognized  
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9 115 proxy for the presence of chronic diseases using data on medications bills that were reimbursed  
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11 116 [24]. The Swiss healthcare system offers different cost-sharing options to patients, including  
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13 117 low (CHF 500, 1000) or high deductibles (i.e., CHF 1500, 2000, or 2500), and integrated care  
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15 118 models, which offer premium rebates in exchange for limited healthcare provider options. Thus,  
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17 119 having a low (CHF 500, 1000) or high deductible (i.e., CHF 1500, 2000, or 2500 vs. CHF 300),  
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19 120 and being enrolled in a managed care model were used in the analysis. Prescribed medications  
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21 121 were characterized by category (fusion proteins, hormones, monoclonal antibodies, low-  
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23 122 molecular-weight [LMW] heparins and growth factors), whether there were multiple packaging  
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25 123 sizes, the cost per package of the reference product (in CHF, <100, 100-599, >600), relative  
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27 124 price difference of the reference product to the corresponding biosimilar (<10, 10-19, >20), and  
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29 125 the number of available imitator drugs (1, 2, >2) at the date of prescription. The analysis adds  
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31 126 the aspect of healthcare provider by including information on the supply channel (general  
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33 127 practitioner, outpatient hospital, specialist, traditional pharmacy).  
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35 128 To ensure consistent terminology, we referred to all biologically manufactured drugs as  
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37 129 "biological products", while the originator drugs are referred to as "biologics" or as "reference  
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39 130 products", and imitator products as "biosimilars" throughout the manuscript.  
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### 49 131 **Statistical analysis**

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52 132 All statistical analysis were performed at the study population that consisted of individuals who  
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54 133 had at least one biosimilar available on the market at the time of IP of a biologic product. All  
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56 134 research participants' baseline characteristics are shown as counts and percentages, or as mean  
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58 135 and standard deviation for continuous variables. We compared patient characteristics for all  
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3 136 individuals with and without biosimilar IP. For bivariate comparisons between patients with  
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5 137 and without biosimilar IP, Fisher exact and Chi-Square tests were used accordingly. Statistical  
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7 138 significance was defined as a two-sided p-value of 0.05. We determined the biosimilar  
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10 139 prevalence by distinguishing between IP and FP and the prevalence of biological therapy  
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12 140 switches (number of prescriptions and patients) for each year (2016-2021). Chi-squared tests  
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14 141 were used to determine whether the prevalence of biosimilars among all patients using a  
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16 142 biological product was equivalent across the years. To assess the determinants of biosimilar  
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18 143 prescriptions, we used logistic regression models in which the dependent variable was whether  
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20 144 a biosimilar was prescribed as IP (0 or 1). We employed three distinct logistic regression  
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22 145 models, each incorporating an additional set of variables, to comprehensively assess the impact  
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24 146 of various factors on our study outcomes (Table A8 in supplementary file). This approach  
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26 147 allows us to explore multiple dimensions of influence and gain a more nuanced understanding  
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28 148 of the relationships at play, enhancing the robustness and depth of our analysis. Both, Model B  
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30 149 (sociodemographic + medication variables) and C (sociodemographic + medication + provider  
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32 150 variables), show similar results and a better fit of the estimates compared to Model A  
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34 151 (sociodemographic variables) based on the goodness-of-fit criteria (AIC, BIC). For the  
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36 152 manuscript, we proceed with Model C because we are mainly interested in the associations with  
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38 153 biosimilar prescriptions from all three points of view (patient, medication, physician). Odds  
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40 154 ratios (OR) and corresponding 95% confidence intervals (CI) were calculated for each  
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42 155 regression coefficient. The success rate in the binomial model was denoted by the term  
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44 156 "occurrence" to improve the results' readability. All analyses were performed using R version  
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46 157 4.2.1.

### 158 **Patient and public involvement**

159 None.

## 160 RESULTS

161 This research was conducted using a study population comprising 68,310 individuals who  
 162 received at least one prescription for a biological or biosimilar medication between 2016 and  
 163 2021. For our study, we eliminated individuals who did not maintain continuous mandatory  
 164 health insurance coverage throughout the entire observation period. This exclusion was  
 165 implemented to mitigate potential bias in our regression analysis, resulting in a remaining  
 166 sample size of 53,379 patients. Within this subgroup, there were 18,953 instances of initial  
 167 prescriptions for biological medications that had a biosimilar alternative available at the time  
 168 of dispensing.

169 In the study sample we observed 18,953 first prescriptions of biological products. Patient  
 170 characteristics of the study population at the time of IP, stratified by type of IP (reference  
 171 product 81.5%, biosimilar 18.5%), are presented in Table 1. Female patients more frequently  
 172 received biosimilars than males (60.6%). The study's overall population demonstrated a  
 173 balanced distribution among age categories (<50, 50-64, 65-74, >74). Notably, individuals  
 174 prescribed reference products as IP were more prevalent in the highest age group, while those  
 175 initially prescribed biosimilars were more concentrated in the 50-64 and 65-74 age group. LMW  
 176 heparins were the most prescribed reference products (54.2%), with growth hormones  
 177 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%)	

<sup>1</sup>) Fisher exact test, <sup>2</sup>) Chi-Square test

Signif. codes: '\*\*\*' 0.001

178 Table 2 describes the overall frequency of biologicals products over the observation period  
 179 including the absolute and relative frequency of biosimilars in comparison to all biological  
 180 prescriptions. Of all biological products (IP and FP), 28.6% were biosimilar prescriptions. In  
 181 absolute values, the prescription rate of biosimilars increased over time (from 1016 in 2016 to  
 182 6976 in 2021). However, there is no discernible trend in the relative share of biosimilars in all  
 183 prescriptions of biological products (35.5% in 2016, 39.2% in 2017, 45.2% in 2018, 41.6% in  
 184 2019, 26.3% in 2020 and 22.5% in 2021). Furthermore, the share of biosimilars in FPs was  
 185 higher than in IPs in every year. The growth factor Filgrastim was the most frequently prescribed  
 186 active substance of biosimilars in IPs and FPs (53.1% and 36.2% respectively), while  
 187 enoxaparin was the most frequently prescribed active substance of reference products in IPs  
 188 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	
<b>IP</b>								
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
<b>FP</b>								
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
<b>Total (FP+IP)</b>								
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

Chi-Square test, Signif. codes: '\*\*\*' <0.001

189 Of the study population, only a small subset (n=1492, 8.5%) experienced at least one  
 190 medication switch (Table 3). Most patients had switches between reference products (n=867,  
 191 58.1%), followed by switches from reference product to biosimilar (n=331, 22.2%), from  
 192 biosimilar to reference product (n=297, 19.9%) and switches between biosimilars (n=286,  
 193 19.2%). The number of patients with at least one switch increased between 2016 and 2021

194 (from 28 to 662), whereby the numbers of patients with switches between reference products  
 195 increased most prominently (from 25.0% in 2016 to 62.1% in 2021). Switches between  
 196 reference products and between biosimilars occurred most often for Enoxaparin and Rituximab,  
 197 respectively (Table A7 in supplementary file). The most common switches from reference  
 198 product to biosimilar and from biosimilar to reference products were most often observed for  
 199 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

Chi-Square test  
 Signif. codes: '\*\*\*' <0.001

200 As far as the regression results are concerned, the odds of prescribing biosimilars at IP have  
 201 been increasing over the years (Fig.1, Table A8 in supplementary file). Male sex was associated  
 202 with 13.2% higher odds of receiving biosimilar IP, whereas residence in a French or Italian-  
 203 speaking region had a 38.9% and 23.9%, respectively, lower occurrence of a biosimilar IP.  
 204 None of the insurance-related variables showed a significant association with biosimilars IPs.  
 205 In terms of pharmaceutical variables, monoclonal antibodies, LMW heparins and growth  
 206 factors were associated with substantially lower biosimilar IP occurrences (-88.5%, -99.9% and  
 207 -84.2%) than fusion proteins. The availability of multiple packaging sizes was associated with  
 208 4.6-fold higher odds of biosimilar IP compared to medications with solely one packaging size.  
 209 For the absolute package price, no consistent pattern was observed, as medications with prices

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3 210 between 100 and 599 francs per pack decreased the odds by 79.8% compared to the baseline  
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5 211 (<100 CHF), whereas the odds in the highest prize category (>600 CHF) were lower by 34.3%.  
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7 212 However, compared to products with a <10% price difference between reference product and  
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9 213 biosimilar, higher price reductions were associated with decreased occurrence of biosimilar IP:  
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11 214 medications with 10-19% price difference had 92.4% lower odds and medications with more  
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13 215 than 20% had even 93.3% lower odds. On the contrary, increasing the number of available  
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15 216 imitator medications of prescription (2 and >2) had substantially higher (2.36-fold and 9.65-  
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17 217 fold) odds of biosimilar IP compared to prescriptions with only one available biosimilar. As far  
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19 218 as provider variables are concerned, physicians in the outpatient hospital setting prescribed far  
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21 219 more biosimilars compared to general practitioners (2.48-fold higher odds). The occurrence of  
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23 220 biosimilar IP was also 41.7% higher in patients who had been prescribed biological products  
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25 221 by a specialist than in patients who had received the equivalent medications from a general  
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27 222 practitioner.  
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## 35 223 **DISCUSSION**

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38 224 The increase in biosimilar prescriptions over time can be attributed to the growing biosimilar  
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40 225 market. With 15 approved biosimilars in 2016, this market has expanded significantly, reaching  
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42 226 78 biosimilars in 2021 (Table A1 in supplementary file) [8, 21]. A longer time on the market  
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44 227 gives the biosimilar a better chance to establish itself and gain market share. Despite this  
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46 228 growth, the biosimilars' claims in Switzerland remained relatively low. In 2021, claims for  
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48 229 reference products were four times higher than claims for biosimilars among all available  
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50 230 biological products with biosimilars. [8]. Comparatively, other countries like Norway have  
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52 231 achieved 80% biosimilar quota of all biologic products[25], while in Germany, studies reported  
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54 232 an average biosimilar ratio between 40.5% and 51.9% in 2019[26, 27]. In the present study we  
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56 233 observed substantially lower average biosimilar quota of 28.0%. Infliximab is a particularly  
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3 234 compelling example, with the biosimilar share reaching 26% in Germany after only 12 months  
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5 235 on the market (2017) and rising to 64-68% of the biosimilar market in 2019. By contrast,  
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7 236 infliximab achieved a market share of only 22% in Switzerland in 2019 [8].  
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10 237 The low biosimilar market share in Switzerland can be attributed to several factors, including  
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12 238 physician and patient knowledge deficits regarding biosimilars, leading to reluctance in their  
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14 239 use [12–15]. According to survey studies [20, 28–31], negative perceptions of biosimilars  
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16 240 among 15-30% of the population may be rooted in concerns about the evidence base for their  
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18 241 efficacy and safety, primarily requiring bioequivalence for approval.. However, there is  
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20 242 increasing evidence of equivalent safety and efficacy of biosimilars, along with evidence of  
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22 243 bioequivalence [32–34]. Furthermore, a challenge for newly approved biosimilars is the  
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24 244 difficulty in extending conclusions from RCTs to the broader population that will use the  
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26 245 biosimilar. This is because RCTs typically enroll a more homogeneous population, and certain  
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28 246 patient groups, such as pediatric, elderly, and comorbid populations, as well as patients with  
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30 247 polypharmacy, are often underrepresented in these trials [35–37]. As a result, prescribers may  
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32 248 be skeptical about the use of biosimilars in these patient populations because of the lack of data.  
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34 249 Moreover, the finding that patients frequently switch from biosimilar to reference products  
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36 250 underscores the complex landscape surrounding biosimilar utilization. This phenomenon may,  
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38 251 in part, be influenced by the current incentive system discourages the prescription of biosimilars  
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40 252 for self-dispensing doctors and pharmacies as they are rewarded with larger profit margins for  
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42 253 prescribing the more expensive products [8]. Conversely, under a capitation payment model,  
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44 254 managed care physicians may have a financial incentive to prescribe lower-cost biosimilars in  
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46 255 order to maximize profits. However, if physicians are not properly educated about the safety  
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48 256 and efficacy of biosimilars, they may be hesitant to prescribe them.  
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50 257 That only a small subset (n=1492, 8.5%) experienced at least one medication switch can be  
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52 258 explained by the reluctance of patients to switch to a biosimilar medication due to the fear of  
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3 259 experiencing new and unknown side effects. Patients who have been using a particular  
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5 260 medication for a long time and have become accustomed to its efficacy and safety profile may  
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7 261 be hesitant to switch to a biosimilar, which they perceive as being different and possibly  
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9 262 inferior. Nevertheless, efficacy of biosimilar switching has been observed [8, 32–34, 38, 39].  
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11 263 According to a systematic literature review based on 90 published studies, the great majority of  
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13 264 the publications did not report differences in immunogenicity, safety, or efficacy when patients  
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15 265 switched to biosimilars. Three large studies did not show differences in efficacy or safety after  
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17 266 multiple switches between reference product and biosimilar [40–42]. Only two publications  
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19 267 reported a loss of efficacy or increased dropout rates [43, 44]. Often, this very knowledge and  
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21 268 awareness about the safety and efficacy of switching to new treatment options lack for  
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23 269 prescribing physicians who rely on solid, evidence-based data to make treatment decisions [45–  
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25 270 47]. The substantial transition from biosimilars to reference products observed in our study  
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27 271 warrants discussion. While our analysis didn't delve into the specific drivers behind this shift,  
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29 272 several factors may contribute to it. These could encompass the beforementioned patient and  
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31 273 physician preferences. Further exploration of these factors is essential to gain a comprehensive  
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33 274 understanding of the dynamics between biosimilars and reference products in clinical practice,  
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35 275 shedding light on the implications for healthcare stakeholders and policymakers.  
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37 276 The regression results revealed that biosimilar IP rates were lower in French-speaking cantons.  
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39 277 These regional variations may be caused by a variety of variables, including a higher  
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41 278 concentration of medical services in urban regions, various patient characteristics, and cultural  
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43 279 variations between cantons [48, 49]. Our findings showed that biosimilars with high relative  
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45 280 price difference to reference product were less likely prescribed. Several factors contribute to  
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47 281 physicians' reduced prescription rates in association with the lower prices of biosimilars. A  
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49 282 possible explanation is that healthcare providers may have less experience with biosimilars with  
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51 283 a higher price difference or may perceive them as less established and less proven than  
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3 284 biosimilars with a lower price difference. This lack of familiarity or perceived risk may  
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5 285 contribute to reluctance in prescribing biosimilars with a higher price difference. It is also  
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7  
8 286 important to consider the role of financial incentives and reimbursement policies in biosimilar  
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10 287 prescribing: Currently, dispensation channels receive a larger profit margin when distributing  
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12 288 the more expensive reference product under the present price-dependent margin [21]. This  
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14 289 incentive system seems to be characteristic for Switzerland, as studies conducted in European  
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16 290 countries did not find a relationship between price difference and biosimilar dissemination [50–  
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18 291 52]. This might be attributed to several factors that differentiate Switzerland from other  
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20 292 European countries: Cantonal differences in self-dispensing regulation, the country's different  
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22 293 prescribing cultures and guidelines across its language regions, and capitation is implemented  
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24 294 only in relatively few cases in Switzerland. In our analysis, male patients had more biosimilar  
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26 295 IP. According to studies, women were often more skeptical of imitator drugs [28, 53–56] and  
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28 296 they more frequently believe that they are more responsive to medications than men [57–59].  
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30 297 This can have an impact on their confidence in biosimilars, making female patients more aware  
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32 298 of potential side effects or lack thereof. Biosimilar IPs were prescribed more frequently for  
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34 299 fusion proteins compared to other categories which indicates an increased acceptance of  
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36 300 imitator products in this drug class. This is supported by the relatively early market entry (2018)  
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38 301 and by a meta-analysis showing comparable results in terms of efficacy and safety between  
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40 302 reference product and biosimilars [60]. The strongest facilitator of biosimilar prescriptions was  
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42 303 the amount of available biosimilars, which is in line with the findings of a prior study [50, 61].  
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44 304 Thus, the replacement of reference products by biosimilars seems to be better accepted in  
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46 305 market segments with many imitator products. This finding is probably associated with the  
47  
48 306 larger collective promotional effort from multiple players involved in the field to favor  
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50 307 biosimilars; it is noteworthy that the largest adoption of biosimilars (Filgrastim) has been  
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52 308 partially attributable to the fact that numerous biosimilar producers have commercialized  
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3 309 different products, whereas there is only one company branding the reference product [62]. We  
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5 310 found more biosimilar IPs for specialists and outpatient hospital physicians than GP. These  
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7 311 findings are in line with existing literature that showed more biosimilars from specialists who  
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9 312 reported a higher confidence in the comparability of biosimilars than GPs [63, 64]. Differences  
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11 313 in care providers may be due to a variety of reasons: some healthcare providers may not be  
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13 314 interested in stockpiling too many different medications and additional biosimilars, as they  
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15 315 sometimes have large storage requirements (cooling, expiration date) and , thus, are associated  
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17 316 with a significant financial risk [21]. In addition, it has been demonstrated that the dissemination  
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19 317 of knowledge about new prescription options is heterogeneous because there are large learning  
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21 318 costs associated with the treatment effects of new therapy options, which rely on the training  
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23 319 and experience of the doctor [65]. Despite the fact that a previous study conducted in the context  
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25 320 of generic drugs showed that older people are less likely to use imitator products when offered  
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27 321 a choice [28, 61], we did not observe an age-dependency of biosimilar prescriptions.  
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29 322 The most valuable strength of this study is the extensive dataset of biosimilar prescriptions and  
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31 323 potential influencing factors including sociodemographic, pharmaceutical and healthcare  
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33 324 provider variables that were gathered from a representative sample of the Swiss population.  
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35 325 Hence, earlier research has suggested that this database can be considered reasonably  
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37 326 representative of the broader Swiss population, given that the findings revealed only minimal  
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39 327 disparities between unadjusted and adjusted results. The main limitation is the dearth of clinical  
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41 328 data in our database (e.g., disease severity, clinical diagnosis, and reason for biosimilar  
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43 329 utilization). However, we attempted to mitigate this by utilizing comorbidity measures based  
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45 330 on reimbursed prescriptions to control for potential confounders. Furthermore, it is possible that  
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47 331 invoices from individuals whose annual healthcare expenses did not surpass the annual  
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49 332 deductible were not included in the analysis. Nevertheless, internal analyses conducted by  
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51 333 Helsana indicated that this proportion accounts for approximately 1.5% of invoices, suggesting  
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3 334 that any potential selection bias is likely minimal. Another limitation of our study is that the  
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5 335 follow-up period for the prescriptions was limited to 12 months. This time frame may have led  
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7 336 to the exclusion of some prescriptions, potentially introducing bias into our results.  
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10 337 Nevertheless, we observed that a significant number of patients (7608, which accounts for  
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12 338 43.1% of the total) were given only one prescription, indicating that any bias arising from this  
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14 339 limitation is expected to be insignificant.

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17 340 It is worth noting that the actual biosimilars quota (proportion of biosimilars claims relative to  
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19 341 overall biological product claims), is lower in reality as there are biological products for  
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21 342 which no corresponding biosimilars are available on the market. Nevertheless, even when  
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23 343 considering this relatively higher observed quota, it remains comparatively low compared to  
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25 344 other EU countries. This has important implications for the adoption and utilization of these  
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27 345 products in Switzerland. Patients and physicians should be better and objectively informed  
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29 346 about biosimilars in order to increase the acceptance [47, 48]. Also, for example, a clear and  
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31 347 conspicuous indication of the prescribed active substance on the medication package for both  
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33 348 the reference product and the imitator drug, for instance, could enhance patient confidence  
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35 349 [42]. To address the perceived uncertainty and mistrust in imitator products, the evidence base  
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37 350 should be further strengthened: direct evidence to help explain some of the practical aspects  
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39 351 related to the use of biosimilars can be provided by retrospective studies, national databases  
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41 352 and registries that track the long-term immunogenicity and safety of biosimilars [66–71]. In  
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43 353 addition, the incentive system for healthcare providers seems to be designed in such a way  
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45 354 that fewer biosimilars are prescribed. Thus, these incentives should be eliminated, for  
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47 355 example by introducing a fixed margin that always remunerates the medication supplier the  
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49 356 same regardless of the prescribed product (reference product or biosimilar). In order to exploit  
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51 357 the cost saving potential of biosimilars, the aforementioned measures should be targeted to  
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53 358 biosimilars with a noticeable price difference compared to their reference products, and that  
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3 359 still possess relatively low biosimilar market share. Taking into account the findings  
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5 360 presented in Table A6 (in supplementary file), notable examples of these biosimilars include  
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7 361 bevacizumab, follitropin alfa, and pegfilgrastim.  
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10 362 However, the decision to prescribe an imitator drug should not merely be motivated by the  
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12 363 cost-saving potential but should ensure appropriate health care provision for the patients.  
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14 364 Therefore, it is crucial for healthcare providers to engage in shared-decision making with their  
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16 365 patients to determine the most appropriate treatment option based on their individual medical  
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18 366 situation.  
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## 23 367 **CONCLUSION**

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26 368 Despite an increase of available biosimilars in Switzerland between 2016 and 2021, the  
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28 369 biosimilars market share remained relatively low over time. In addition, biological therapy  
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30 370 switches were rarely observed, highlighting the importance of IPs. Our study suggests that  
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32 371 greater acceptance and higher utilization of biosimilars may be associated with the availability  
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34 372 of different package sizes and lower price differences between biosimilars and their reference  
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36 373 products. Patients and providers should be informed about biosimilars in a timely and  
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38 374 appropriate manner, and outdated incentive structures have to be changed to increase the use of  
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42 375 biosimilars.  
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2  
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4  
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6  
7 380 additional role in the study design, data collection and analysis, decision to publish, or  
8  
9 381 preparation of the manuscript.  
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15  
16 383 management. MN and KW performed the statistical analyses, with the contribution of SB, CH  
17  
18 384 and EB. KW drafted the main manuscript text. All authors assisted in the interpretation of the  
19  
20 385 results and critically revised the manuscript. All authors have read and approved the manuscript.  
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26 386 **Data availability statement** Helsana provides the data that support up the findings of this  
27  
28 387 research. (<https://www.helsana.ch/en/helsana-group>). These data, which were used under  
29  
30 388 license for the present study and are not accessible to the general public, are subject to  
31  
32 389 restrictions. But with Helsana's consent and upon reasonable request, data are available from  
33  
34 390 the authors ([gesundheitskompetenz@helsana.ch](mailto:gesundheitskompetenz@helsana.ch)).  
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40 **Ethics approval** The data used in this study were retrospective, pre-existing, de-identified, and  
41  
42 anonymous in accordance with privacy laws and regulations. This study was free from the  
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44 provisions of the Swiss Federal Law on Human Research because it used retrospective, de-  
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46 identified, and anonymized data (Humanforschungsgesetz) [72] and was thus exempted from  
47  
48 receiving clearance from the regional ethics committee (the ethical committee of the Canton of  
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50 Zurich) as well as from obtaining the patients' informed consent.  
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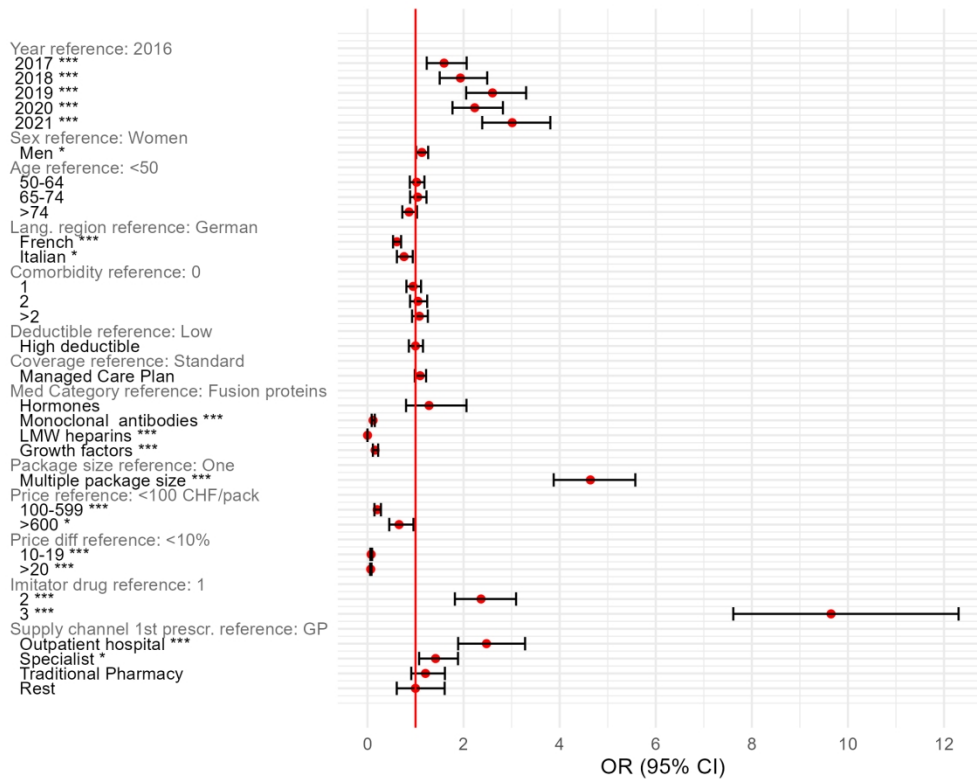


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## FIGURE TITLE

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48 622 **Figure 1.** Determinants of biosimilar initial prescription (logistic regression)  
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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)
<i>Low-molecular-weight heparins</i>							
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
<i>Growth factors</i>							
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	Epex	0.008 / 6	71.5	Binocrit	01.10.2009	0.008 / 6	66.15
B03	Epex	0.017 / 6	126.55	Binocrit	01.10.2009	0.017 / 6	115.7
B03	Epex	0.025 / 6	181.65	Binocrit	01.10.2009	0.025 / 6	165.25
B03	Epex	0.037 / 6	236.75	Binocrit	01.10.2009	0.037 / 6	214.7
B03	Epex	0.046 / 6	291.8	Binocrit	01.10.2009	0.046 / 6	264.5
B03	Epex	0.092 / 6	567.2	Binocrit	01.10.2009	0.092 / 6	512.1
<i>Hormones</i>							
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
<i>Fusion proteins</i>							
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

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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	Model B: Model A + medication variables	Model C: Model B + provider variables
	OR [95%CI]	OR [95%CI]	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]



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3	Age:			
4	<50 (reference)			
5	50-64	1.302 [1.169, 1.452]	1.005 [0.867, 1.164]	1.022 [0.881, 1.185]
6	65-74	1.571 [1.401, 1.761]	1.044 [0.889, 1.227]	1.044 [0.887, 1.228]
7	>74	0.961 [0.849, 1.086]	0.825 [0.694, 0.98]	0.864 [0.725, 1.03]
8	Language region			
9	German (reference)			
10	French	0.578 [0.521, 0.64]	0.582 [0.51, 0.664]	0.611 [0.532, 0.7]
11	Italian	0.467 [0.397, 0.546]	0.744 [0.601, 0.918]	0.761 [0.612, 0.942]
12	Number of comorbidity:			
13	0 (reference)			
14	1	1.054 [0.932, 1.191]	0.934 [0.796, 1.094]	0.95 [0.81, 1.115]
15	2	1.095 [0.963, 1.244]	1.041 [0.88, 1.23]	1.05 [0.886, 1.243]
16	>2	0.938 [0.837, 1.051]	1.05 [0.904, 1.22]	1.08 [0.928, 1.256]
17	Deductible:			
18	Low (reference)			
19	High	1.067 [0.954, 1.192]	1.005 [0.868, 1.163]	0.998 [0.861, 1.155]
20	Managed care	1.029 [0.949, 1.116]	1.103 [0.992, 1.226]	1.095 [0.984, 1.22]
21	Category:			
22	Fusion proteins (reference)			
23	Hormones		1.297 [0.816, 2.081]	1.281 [0.803, 2.06]
24	Monoclonal antibodies		0.152 [0.116, 0.199]	0.115 [0.087, 0.152]
25	Low-molecular-weight heparins		0.001 [0.001, 0.001]	0.001 [0, 0.001]
26	Growth factors		0.235 [0.168, 0.327]	0.158 [0.112, 0.222]
27	Multiple package size		4.551 [3.808, 5.461]	4.64 [3.876, 5.575]
28	Cost per package of reference			
29	product (in CHF)			
30	<100			
31	100-599		0.254 [0.185, 0.349]	0.202 [0.145, 0.28]
32	>600		0.853 [0.592, 1.236]	0.657 [0.453, 0.957]
33	Relative price difference (%)			
34	<10			
35	10-19		0.091 [0.072, 0.115]	0.076 [0.059, 0.096]
36	>20		0.067 [0.053, 0.084]	0.067 [0.054, 0.084]
37	Number of available imitator drug:			
38	1 (reference)			
39	2		2.15 [1.671, 2.785]	2.363 [1.819, 3.093]
40	>2		8.143 [6.502, 10.248]	9.649 [7.614, 12.303]
41	Suppl			
42	General practitioner (reference)			
43	Outpatient hospital			2.477 [1.887, 3.28]
44	Specialist			1.417 [1.075, 1.884]
45	Traditional pharmacy			1.207 [0.911, 1.611]
46	Rest			0.998 [0.609, 1.606]
47	Observations	18'953	18'953	18'953
48	AIC	16'588	9'868	9'735
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# 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
<b>Title and abstract</b>		
Title	<a href="#">#1a</a> Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	<a href="#">#1b</a> Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
<b>Introduction</b>		
Background / rationale	<a href="#">#2</a> Explain the scientific background and rationale for the investigation being reported	4,5

1	Objectives	<a href="#">#3</a>	State specific objectives, including any	4,5
2			prespecified hypotheses	
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6	<b>Methods</b>			
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10	Study design	<a href="#">#4</a>	Present key elements of study design early in the	5,6,7
11			paper	
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15	Setting	<a href="#">#5</a>	Describe the setting, locations, and relevant	5,6,7
16			dates, including periods of recruitment, exposure,	
17			follow-up, and data collection	
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23	Eligibility criteria	<a href="#">#6a</a>	Give the eligibility criteria, and the sources and	5,6
24			methods of selection of participants. Describe	
25			methods of follow-up.	
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30	Eligibility criteria	<a href="#">#6b</a>	For matched studies, give matching criteria and	n/a. The resent study
31			number of exposed and unexposed	does not contain
32				matched studies
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38	Variables	<a href="#">#7</a>	Clearly define all outcomes, exposures,	5,6,7
39			predictors, potential confounders, and effect	
40			modifiers. Give diagnostic criteria, if applicable	
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46	Data sources /	<a href="#">#8</a>	For each variable of interest give sources of data	3,4
47	measurement		and details of methods of assessment	
48			(measurement). Describe comparability of	
49			assessment methods if there is more than one	
50			group. Give information separately for for	
51			exposed and unexposed groups if applicable.	
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1	Bias	<a href="#">#9</a>	Describe any efforts to address potential sources	6,7
2			of bias	
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6	Study size	<a href="#">#10</a>	Explain how the study size was arrived at	5,6
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9	Quantitative	<a href="#">#11</a>	Explain how quantitative variables were handled	5,6,7
10	variables		in the analyses. If applicable, describe which	
11			groupings were chosen, and why	
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17	Statistical	<a href="#">#12a</a>	Describe all statistical methods, including those	7,8
18	methods		used to control for confounding	
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22	Statistical	<a href="#">#12b</a>	Describe any methods used to examine	7,8
23	methods		subgroups and interactions	
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28	Statistical	<a href="#">#12c</a>	Explain how missing data were addressed	8
29	methods			
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33	Statistical	<a href="#">#12d</a>	If applicable, explain how loss to follow-up was	8
34	methods		addressed	
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38	Statistical	<a href="#">#12e</a>	Describe any sensitivity analyses	n/a
39	methods			
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44	<b>Results</b>			
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47	Participants	<a href="#">#13a</a>	Report numbers of individuals at each stage of	8
48			study—eg numbers potentially eligible, examined	
49			for eligibility, confirmed eligible, included in the	
50			study, completing follow-up, and analysed. Give	
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1		information separately for exposed and	
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3		unexposed groups if applicable.	
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6	Participants	<a href="#">#13b</a> Give reasons for non-participation at each stage	8
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9	Participants	<a href="#">#13c</a> Consider use of a flow diagram	n/a, addressed in text
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11			at page 4
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14	Descriptive data	<a href="#">#14a</a> Give characteristics of study participants (eg	8,9
15		demographic, clinical, social) and information on	
16		exposures and potential confounders. Give	
17		information separately for exposed and	
18		unexposed groups if applicable.	
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26	Descriptive data	<a href="#">#14b</a> Indicate number of participants with missing data	n/a. We excluded
27		for each variable of interest	missing data before
28			descriptively
29			analysing the study
30			population
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38	Descriptive data	<a href="#">#14c</a> Summarise follow-up time (eg, average and total	8,9,10,11
39		amount)	
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44	Outcome data	<a href="#">#15</a> Report numbers of outcome events or summary	8,9,10,11
45		measures over time. Give information separately	
46		for exposed and unexposed groups if applicable.	
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51	Main results	<a href="#">#16a</a> Give unadjusted estimates and, if applicable,	8,9,10,11
52		confounder-adjusted estimates and their	
53		precision (eg, 95% confidence interval). Make	
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1		clear which confounders were adjusted for and	
2		why they were included	
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6	Main results	<a href="#">#16b</a> Report category boundaries when continuous	8,9,10,11
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8		variables were categorized	
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11	Main results	<a href="#">#16c</a> If relevant, consider translating estimates of	12
12			
13		relative risk into absolute risk for a meaningful	
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15		time period	
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18	Other analyses	<a href="#">#17</a> Report other analyses done—eg analyses of	n/a
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20		subgroups and interactions, and sensitivity	
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22		analyses	
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26	<b>Discussion</b>		
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29	Key results	<a href="#">#18</a> Summarise key results with reference to study	13
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31		objectives	
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35	Limitations	<a href="#">#19</a> Discuss limitations of the study, taking into	17
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37		account sources of potential bias or imprecision.	
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39		Discuss both direction and magnitude of any	
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41		potential bias.	
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45	Interpretation	<a href="#">#20</a> Give a cautious overall interpretation considering	13,14,15,16
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47		objectives, limitations, multiplicity of analyses,	
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49		results from similar studies, and other relevant	
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51		evidence.	
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55	Generalisability	<a href="#">#21</a> Discuss the generalisability (external validity) of	17
56			
57		the study results	
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1 Other

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3 Information

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5  
6 Funding [#22](#) Give the source of funding and the role of the 19  
7 funders for the present study and, if applicable,  
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9 for the original study on which the present article  
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11 is based  
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16 Notes:

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19  
20 • 6b: n/a. The present study does not contain matched studies  
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23 • 13c: n/a, addressed in text at page 4  
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26 • 14b: n/a. We excluded missing data before descriptively analysing the study population  
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29 • 20: 13,14,15,16 The STROBE checklist is distributed under the terms of the Creative Commons  
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33 [Penelope.ai](#)  
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