Temporal trends in the prescription of biosimilars and the status of switching from original biologics to biosimilars at individual and institutional levels in Japan

Running head: Temporal trends in biosimilar prescriptions in Japan

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39 utilization, administrative claims

40

41 **Abstract**

42 **Purpose:** To describe the temporal trends in the prescription of biologics in Japan, with
43 additional analysis focusing on switching from original biologics to biosimilars at the
44 individual and institutional levels.

45 **Methods:** Using the JMDC claims database from January 2005 to May 2024, we identified
46 patients who received at least one prescription for 17 biologics (original biologics or
47 biosimilars). We elucidated the monthly trends in the proportions of original biologics and
48 biosimilars. We also estimated the proportion of patients receiving original biologics only,
49 those receiving biosimilars only, and those switching from original biologics to biosimilars
50 (and vice versa) during the study period. Finally, we estimated the proportion of medical
51 institutions that started prescribing biosimilars during the study period based on the type of
52 medical institution.

53 **Results:** Temporal trends in the proportions of original biologics and biosimilars varied widely.
54 In May 2024, the proportion of biosimilar prescriptions was 13.6% for somatropin and 92.5%
55 for filgrastim. At the individual level, the proportion of patients switching from original
56 biologics to biosimilars was low (1.2–14.0%), indicating that switches do not often occur
57 within the same patient, while more recent new users of biologics start biosimilars. At the
58 institutional level, university-related hospitals and clinics were more and less likely,
59 respectively to introduce biosimilars than public and other types of hospitals.

60 **Conclusion:** Temporal trends in the prescription of biosimilars and switching patterns varied
61 widely by the type of biologics. The type of medical institution should be considered when
62 assessing and promoting the use of biosimilars.
63

Introduction

Increasing medical costs has become a global social concern. Prescribed drugs, which account for a considerable part of medical costs, have received attention for potentially reducing its costs [1]. Generic drugs play a pivotal role in reducing drug costs and easing drug budgets [2].

Biologics currently occupy the top positions in drug sales [3]. Biologics are large and complex molecules with structural heterogeneity that have been developed for managing various diseases, including rare diseases [4]. Recently, a group of biologics known as "biosimilars" have been developed to potentially replace high-cost biologics [5]. Biosimilars are biotechnological products that are expected to be comparable to an already approved biotechnological product (referred to as "original biologics") in terms of quality, efficacy, and safety [6].

Although the global market share of biosimilars is steadily increasing with efforts of governments and industries [7,8], biosimilars have not fully penetrated the biologic market, probably due to concerns of healthcare professionals' and patients' regarding their real-world effectiveness and safety [9,10]. A previous systematic review targeting the US and Europe reported that the acceptance of biosimilars varied according to the therapeutic classes [11].

Understanding the trends in the prescription of original biologics and biosimilars is crucial and can be considered the first step towards increasing the use of biosimilars worldwide, including Asia. In addition, researchers and policymakers should understand switches from

original biologics to biosimilars at the individual and institutional levels. Replacement of certain original biologics by biosimilars in certain situations or settings, suggesting potential areas for improvement. To our knowledge, no Asian study has systematically assessed the temporal trends and switching patterns from original biologics to biosimilars, covering a variety of biologics [12].

In the present study, we aimed to describe the temporal trends in the prescription of original biologics and biosimilars in Japan, and performed an additional analysis focusing on switching from original biologics to biosimilars at individual and institutional levels.

Methods

Data Source

We used data from the JMDC claims database, which has been previously described in detail [13]. Briefly, the JMDC claims database is a large-scale database containing medical claims of large- and medium-sized company employees and their dependent family members aged <75 years. Since 2005, the number of individuals in the JMDC database has increased consistently, reaching a cumulative total of more than 20 million by the end of 2024. The JMDC database includes all the monthly claims for outpatient and inpatient diagnoses and procedures, prescriptions, and dispensations of drugs recorded as the Japanese original drug codes and product names, and the World Health Organization Anatomical Therapeutic Chemical (ATC)

102 classification [14]. In addition, the data included the anonymized IDs of medical institutions,
103 with which we could discern which drug was prescribed by the medical institution, as well as
104 the type of medical institution: clinics (defined in Japan as medical institutions with no or <20
105 beds for hospitalization), university-related hospitals, public hospitals, and other hospitals
106 (including private hospitals receiving reimbursement from the health insurance system in
107 Japan). We employed the most recent dataset, extracted in December 2024, which included
108 data from January 2005 to May 2024. The data used in this study were anonymized and
109 processed anonymously by JMDC, Inc.

110 For comparison, we also used the National Database (NDB) Open Data of Health
111 Insurance Claims from April 2022 to March 2023, which is a summary table of the total use of
112 drugs compiled by the government [15] and covers all Japanese citizens except those living
113 with public financial assistance.

114 This study was approved by the Ethics Committees of the University of Tsukuba,
115 Ibaraki, Japan (approval number 2099) and Meiji Pharmaceutical University, Tokyo, Japan
116 (approval number 202462). The analyses were conducted independently at each study location
117 to verify and obtain similar results.

118

119 ***Study population***

120 We identified patients receiving at least one prescription of all 17 biologics (for which

121 biosimilars were approved and marketed by 2024) available in Japan during the study period,
122 including somatropin, erythropoietin (including both epoetin alfa and epoetin beta), filgrastim,
123 infliximab, insulin glargine, rituximab, etanercept, trastuzumab, agalsidase beta, bevacizumab,
124 darbepoetin alfa, teriparatide, insulin lispro, adalimumab, insulin aspart, ranibizumab, and
125 pegfilgrastim. For each of the 17 biologics, we created a list of product names (based on at
126 least one prescription record in the JMDC database during the study period) using the ATC
127 classification system, classifying them as original biologics or biosimilars (**Supplementary**
128 **Table S1**). In the main analysis, we included all these biologics for our analysis. However, for
129 several biologics (somatropin, erythropoietin, insulin glargine, darbepoetin alfa, insulin lispro,
130 and insulin aspart), the original biologics other than the reference product of the biosimilar
131 were approved (**Supplementary Table S1**). Thus, in the sensitivity analysis, we restricted the
132 analysis to biologics and their reference products. In addition, there is one authorized generic
133 (AG) biologic drug for darbepoetin alfa in Japan, which does not have a brand name on its
134 label but is composed of the same drug component as the original biologics [16]. We included
135 this AG biological drug in the biosimilars in the main analysis, but excluded it from our
136 sensitivity analysis.
137
138 ***Data analysis***
139 After summarizing the demographics (age and sex) of the study population by biologics, we

estimated and illustrated the monthly trends in the proportion of prescriptions of original biologics and biosimilars (among the total prescriptions for each biologic) from January 2005 to May 2024. In addition, we compared the statistics (i.e., the number and proportion of biosimilars among the total prescriptions for each biologic) in the JMDC database with those estimated from the NDB Open Data of Health Insurance Claims from April 2022 to March 2023 [15].

Next, at the individual level, we estimated the proportions of (i) patients receiving original biologics only, (ii) those receiving biosimilars only, (iii) those switching from original biologics to biosimilars, (iv) those switching from biosimilars to original biologics, and (v) unknown (because both original biologics and biosimilars were prescribed in the same month, we could not determine which was prescribed earlier from the monthly claims alone) during the study period from January 2005 to May 2024 in the main analysis. Additionally, we restricted the period of the analysis from the time each biosimilar entered the Japanese market to May 2024.

Finally, at the institutional level, among medical institutions with at least one prescription of original biologics, we estimated the proportion of medical institutions starting the prescription of biosimilars during the study period by the type of medical institution (clinics, university-related hospitals, public hospitals, and other hospitals) and 17 biologics.

All the analyses were performed using STATA version 17 software (StataCorp,

College Station, TX, USA).

Results

The number of study patients and their demographics varied by biologics, from 102 for agalsidase beta (mean age 38.3 ± 15.4 years, male 56.9%) to 62,038 for insulin glargine (mean age 52.0 ± 12.8 years, male 66.6%) (**Table 1**). In terms of the total number of prescriptions, insulin was most commonly prescribed (insulin glargine, 1,340,426 times; aspart, 1,173,924 times; and lispro, 1,151,886 times), followed by filgrastim (306,931 times). In the sensitivity analyses restricted to biosimilars (excluding AG biologic drugs) and their reference products, the total number of prescriptions decreased, especially for somatropin and darbepoetin alfa.

The monthly trends in the proportion of original biologics and biosimilars varied widely among biologics (**Fig 1**). Some biologics, such as filgrastim and trastuzumab, demonstrated a steep increase in the proportion of biosimilars since their launch, whereas biologics, such as somatropin and infliximab, demonstrated a slow increase. Darbepoetin alpha and insulin lispro initially demonstrated a steep increase, which became nearly flat. In May 2024, the proportion of biosimilar prescriptions (among all prescriptions of biologics) ranged from 13.6% for somatropin to 92.5% for filgrastim.

The statistics in the JMDC claims database and the NDB Open Data from April 2022 to March 2023 were mostly similar (**Supplementary Table S2**), suggesting the generalizability

178 of the findings in the present study.

179 **Supplementary Table S3** and **Fig 2** illustrate the distribution of patients receiving
180 original biologics only, biosimilars only, and those switching from original biologics to
181 biosimilars, or vice versa. The proportion of patients switching from the original biologics to
182 biosimilars was generally low, varying from 1.2% for erythropoietin to 14.0% for etanercept.
183 The proportion of patients receiving biosimilars only was much higher than that of the patients
184 switching for all biologics, implying that switches do not often occur within the same patient,
185 whereas more recent new users of biologics start with biosimilars. The proportion of patients
186 receiving biosimilars only was the highest for filgrastim (74.4%), followed by darbepoetin alfa
187 (45.4%) and insulin glargine (43.9%). In the additional analysis, restricting the analysis period
188 from when each biologic was launched (to May 2024), the proportion of switchers from the
189 original biologics to biosimilars did not change significantly and remained low, whereas the
190 proportion of patients receiving only biosimilars tended to increase (**Supplementary Table**
191 **S3**).

192 Finally, at the institutional level, for most biologics, the proportion of medical
193 institutions introducing biosimilars during the study period (among those once prescribing
194 original biologics as the denominator) was the highest in university-related hospitals, followed
195 by public hospitals, other hospitals, and clinics (**Fig 3**). However, insulin glargine and
196 darbepoetin alfa were relatively commonly prescribed in all types of medical institutions

197 compared with other biologics.

198

199 **Discussion**

200 This study comprehensively investigated the temporal trends in the prescription of biosimilars,
201 with an additional analysis focusing on switching from the original biologics to biosimilars at
202 the individual and institutional levels, using the JMDC claims database for company employees
203 and their dependent family members. The introduction of biosimilars varied widely by the type
204 of biologics as well as by the type of medical institution. Switching within the same individual
205 was uncommon, whereas more recent new biologics users started using biosimilars only. At the
206 institutional level, university-related hospitals and clinics were more and less likely,
207 respectively, to introduce biosimilars than public and other types of hospitals.

208 The most frequently prescribed biologics were insulin (glargine, aspart, and lispro)
209 merely because diabetes is a common disease, with an estimated 11 million patients in Japan
210 in 2021 [17]. The number of prescriptions of insulin and filgrastim was proportional to the
211 number of patients, while some biologics, such as erythropoietin and pegfilgrastim, were not,
212 suggesting that the frequency and duration of use in individuals vary according to the biologics
213 and related underlying diseases. Restricting our analysis to biosimilars (excluding AG
214 biological drugs) and their reference products, the levels of somatropin and darbepoetin alfa
215 decreased. This suggests that most of the patients treated with somatropin used the original

biologics, which were not the reference products, whereas most of the patients treated with darbepoetin alfa used AG biologic drugs.

The monthly trends in the proportion of biosimilars varied widely according to the biologics. The use of biosimilars filgrastim, rituximab, trastuzumab, ranibizumab, and teriparatide demonstrated rapid increase during the study period. We did not find consistent characteristics that were obviously different between biologics with and without a rapid increase in the proportion of biosimilars, such as the timing of approval and underlying diseases. For example, biosimilars used in cancer treatment, such as filgrastim, rituximab, and trastuzumab, have demonstrated a rapid increase in use; however, bevacizumab (also used in cancer treatment) did not demonstrate a similar trend.

We found some temporal stagnation or a decrease in the proportion of several biologics, such as etanercept, darbepoetin alfa, and filgrastim. One possible explanation is that some practitioners may have stopped using biosimilars owing to a shortage of biosimilars in Japan. Drug shortages occurred for etanercept in 2018 and 2021, darbepoetin alfa in 2020, filgrastim in 2020 and 2022, and pegfilgrastim in 2024. One of the major reasons for drug shortages is that the demand exceeds expectations. A stable supply of biosimilars is necessary to promote their use.

The proportion of switchers from original biologics to biosimilars was generally small. One obvious reason for the low switching proportion within the same individual is that

235 switching from an original biologic to a biosimilar over the course of treatment was not
236 recommended in Japan until 2022 to ensure the traceability of the products as per domestic
237 guidelines. In addition, a previous study reported that some physicians [18] and patients [19]
238 may be concerned about the safety profiles of biosimilars, especially when they switch from
239 the original biologics to biosimilars, which can lead to negative expectations and nocebo effects
240 [20]. A better understanding of biosimilars could help encourage their acceptance by
241 prescribers and patients.

242 The introduction of biosimilars varies according to the type of medical institution. The
243 proportion of clinics that introduced biosimilars was lower than that of the hospitals.
244 University-related hospitals demonstrated the highest proportion of biosimilars. We speculate
245 that hospitals (especially university-related hospitals) may be able to reduce medical costs by
246 introducing biosimilars, or may be more likely to be influenced by the government policy of
247 promoting biosimilars than clinics. As opposed to physicians in hospitals who follow the
248 hospital formulary, physicians in clinics can select any drug based on the preferences of the
249 physician and patient. To increase biosimilar usage, we need to further explore the factors
250 affecting healthcare providers' and patients' acceptance of switching to biosimilars.

251 This study has certain limitations. First, the database comprised large and medium-
252 sized company employees and their family members; thus, the population of this study is
253 expected to be younger and more affluent than the average Japanese population. However, most

biologics are prescribed for patients aged <65 years, and we confirmed that the statistics in the JMDC claims database was generally similar to that obtained from the NDB Open data, which are nationally representative statistics. Second, the present findings from Japan would be informative to, but may not be directly applicable to, other countries because biosimilar usage and switching patterns are affected by various factors such as healthcare policies and reimbursement systems. Finally, although the medical institution IDs and types of medical institutions were variable information in the JMDC claims database, we were unable to obtain other information, such as the area (region) of the medical institutions and the socioeconomic status of the area.

Conclusions

Trends in biologics utilization varied widely between biologics and medical institutions. Data capturing the current use of original biologics and biosimilars in a real-world setting provided the characteristics of biologics, which may contribute to the development of targeted interventions, thus promoting efficient and effective use of biosimilars in the future.

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Author Contributions

MI planned the study and obtained the data. MI, YT, JK, RK, and RS conducted the analysis and created the tables and figures. MM wrote the first draft of the manuscript. AIW, IH, HM, HS, YS, and MA provided critical comments for improving the methods and discussion. All authors have read the final version of the manuscript and have agreed to its submission.

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Figure legends

Fig 1. Monthly trend in the proportion of prescriptions of original biologics (colored gray) or biosimilars (colored black) among the total prescriptions for each biologic during the study period

Note: Although all original biologics or biosimilars available in Japan were included in the main analysis, the sensitivity analysis made the following changes (Supplementary Table S1):

- For somatropin, we considered Genotropin vs. Somatropin BS.
- For erythropoietin, we considered Espo vs. Epoetin Alfa BS (Epoetin Kappa).
- For insulin glargine, we considered Lantus (not including Lantus XR) vs. Insulin Glargine BS.
- For darbepoetin alfa, we considered Nesp vs. Darbepoetin Alfa BS (not including Darbepoetin Alfa authorized generic).
- For insulin lispro, we considered Humalog (not including Humalog Mix and Humalog N) vs. Insulin Lispro BS.
- For insulin aspart, we considered NovoRapid (not including NovoRapid Mix) vs. Insulin Aspart BS.

Fig 2. Distribution of patients receiving only original biologics or biosimilars during the study period or switchers

353 Note: For switchers, only the first switch was assessed and counted (i.e., some patients
354 switched twice or more).
355 Note: Although all original biologics or biosimilars available in Japan were included in the
356 main analysis, the sensitivity analysis made the following changes (Supplementary Table S1):
357 ● For somatropin, we considered Genotropin vs. Somatropin BS.
358 ● For erythropoietin, we considered Espo vs. Epoetin Alfa BS (Epoetin Kappa).
359 ● For insulin glargine, we considered Lantus (not including Lantus XR) vs. Insulin Glargine
360 BS.
361 ● For darbepoetin alfa, we considered Nesp vs. Darbepoetin Alfa BS (not including
362 Darbepoetin Alfa authorized generic).
363 ● For insulin lispro, we considered Humalog (not including Humalog Mix and Humalog N)
364 vs. Insulin Lispro BS.
365 ● For insulin aspart, we considered NovoRapid (not including NovoRapid Mix) vs. Insulin
366 Aspart BS.
367
368 **Fig 3. Distribution of medical institutions prescribing only original biologics (colored**
369 **gray) or original biologics and biosimilars (colored black) during the study period**
370 Note: Although all original biologics or biosimilars available in Japan were included in the
371 main analysis, the sensitivity analysis made the following changes (Supplementary Table S1):

- For somatropin, we considered Genotropin vs. Somatropin BS.
- For erythropoietin, we considered Espo vs. Epoetin Alfa BS (Epoetin Kappa).
- For insulin glargine, we considered Lantus (not including Lantus XR) vs. Insulin Glargine BS.
- For darbepoetin alfa, we considered Nesp vs. Darbepoetin Alfa BS (not including Darbepoetin Alfa authorized generic).
- For insulin lispro, we considered Humalog (not including Humalog Mix and Humalog N) vs. Insulin Lispro BS.
- For insulin aspart, we considered NovoRapid (not including NovoRapid Mix) vs. Insulin Aspart BS.

Table 1. Characteristics of studied drugs and study participants

Name	ATC code	When the original drug was approved in Japan	When the biosimilar was approved in Japan	Total no. of prescriptions during the study period**	No. of patients with ≥1 prescription	Age**, mean ± standard deviation	Sex: no. of male patients (%)
(1) Somatropin	H01AC01	Nov, 1988	Jun, 2009	277238	11264	12.4±11.3	6557 (58.2)
Sensitivity analysis***				80791	3709	11.2±8.9	2185 (58.9)
(2) Erythropoietin	B03XA01	Jan, 1990	Jan, 2010	159167	20175	30.7±27.9	8754 (43.4)
Sensitivity analysis***				112325	14344	27.1±28.1	6312 (44.0)
(3) Filgrastim	L03AA02	Oct, 1991	Nov, 2012	306931	25727	52.1±15.6	12627 (49.1)
(4) Infliximab	L04AB02	Jan, 2002	Jul, 2014	198800	10136	37.3±15.8	6400 (63.1)
(5) Insulin glargine	A10AE04	Oct, 2003	Dec, 2014	1340426	62038	52.0±12.8	41289 (66.6)
Sensitivity analysis***				1017736	51381	52.3±12.6	34487 (67.1)
(6) Rituximab	L01FA01	Jun, 2001	Sep, 2017	87361	8252	51.5±16.2	4868 (59.0)
(7) Etanercept	L04AB01	Jan, 2005	Jan, 2018	192029	7521	49.2±12.0	1203 (16.0)
(8) Trastuzumab	L01FD01	Apr, 2001	Mar, 2018	227537	9136	52.4±9.2	523 (5.7)
(9) Agalsidase beta	A16AB04	Jan, 2004	Sep, 2018	11869	102	38.3±15.4	58 (56.9)
(10) Bevacizumab	L01FG01	Apr, 2007	Jun, 2019	268449	14261	55.0±10.6	5691 (39.9)
(11) Darbepoetin alfa	B03XA02	Apr, 2007	Sep, 2019	131241	13083	55.2±12.6	8480 (64.8)
Sensitivity analysis***				81572	8491	55.0±12.6	5440 (64.1)
(12) Teriparatide	H05AA02	Jul, 2010	Sep, 2019	74155	5345	62.3±8.6	938 (17.6)
(13) Insulin lispro	A10AB04 A10AC04 A10AD04	Aug, 2001	Mar, 2020	1151886	55511	49.8±13.9	32012 (57.7)
Sensitivity analysis***				932485	48537	49.6±14.0	27663 (57.0)
(14) Adalimumab	L04AB04	Apr, 2008	Jun, 2020	196998	10558	40.3±15.1	5655 (53.6)
(15) Insulin aspart	A10AB05	Apr, 2008	Mar, 2021	1173924	49859	49.7±14.7	28693 (57.6)

	A10AD05						
Sensitivity analysis***				971582	44243	49.3±14.8	25123 (56.8)
(16) Ranibizumab	S01LA04	Jan, 2009	Sep, 2021	23925	8160	56.0±12.8	4846 (59.4)
(17) Pegfilgrastim	L03AA13	Sep, 2014	Sep, 2023	93019	19921	53.0±11.0	5367 (26.9)

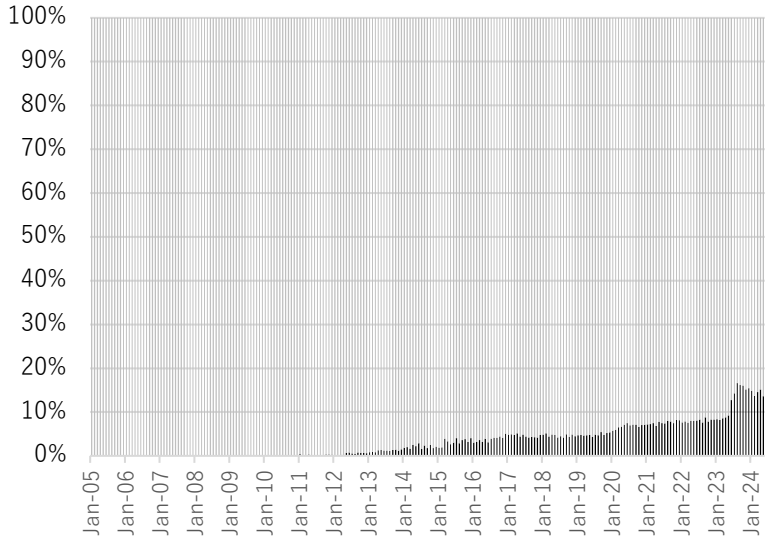
*Age at the time of first prescription in the JMDC claims database.

**From January 2005 to May 2024

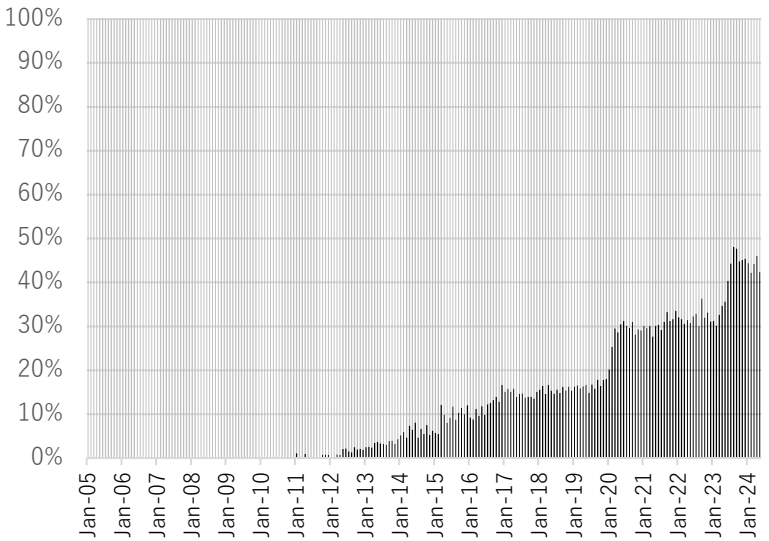
***While all the original biologics or biosimilars available in Japan were included in the main analysis, the sensitivity analysis made the changes below (corresponding to Supplementary Table S1):

- For somatropin, we restricted to Genotropin vs. Somatropin BS.
- For erythropoietin, we restricted to Espo vs. Epoetin Alfa BS (Epoetin Kappa).
- For insulin glargine, we restricted to Lantus (not including Lantus XR) vs. Insulin Glargine BS.
- For darbepoetin alfa, we restricted to Nesp vs. Darbepoetin Alfa BS (not including Darbepoetin Alfa authorized generic).
- For insulin lispro, we restricted to Humalog (not including Humalog Mix and Humalog N) vs. Insulin Lispro BS.
- For insulin aspart, we restricted to NovoRapid (not including NovoRapid Mix) vs. Insulin Aspart BS.

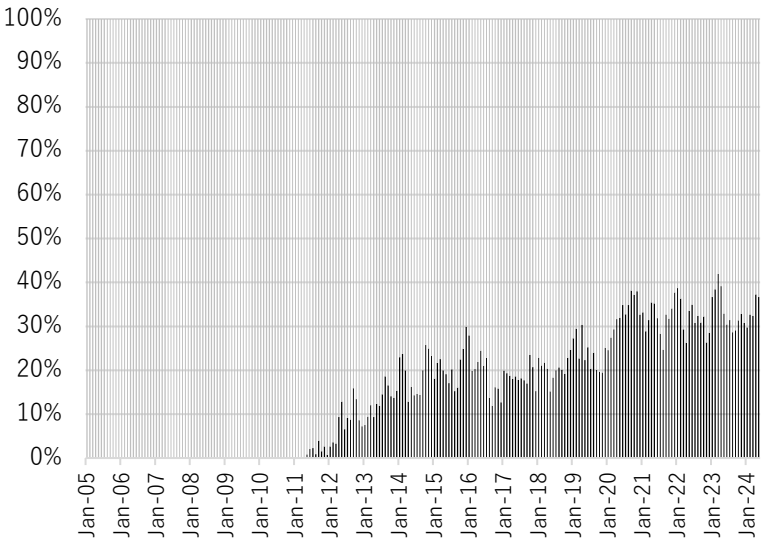
(1) Somatropin



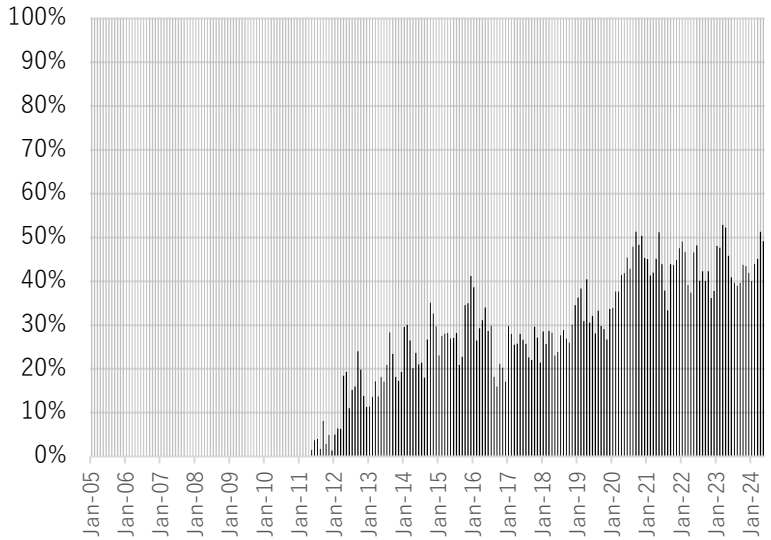
(1) Somatropin: sensitivity analysis



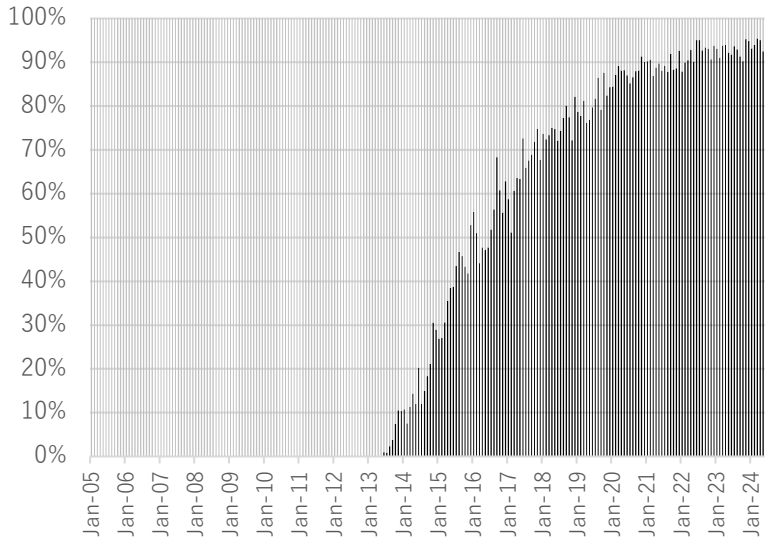
(2) Erythropoietin



(2) Erythropoietin: sensitivity analysis



(3) Filgrastim



(4) Infliximab

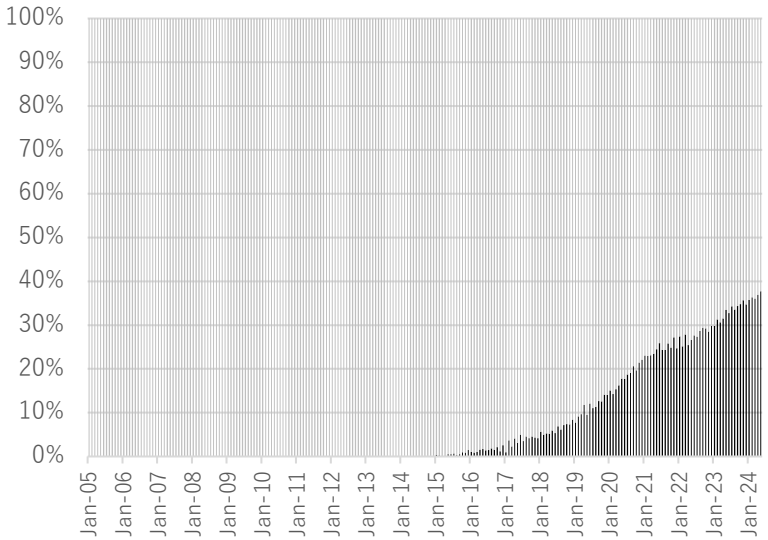
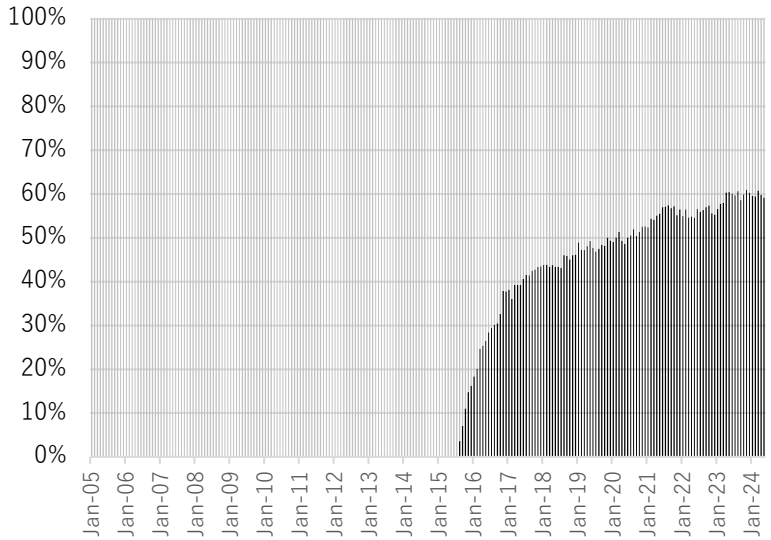
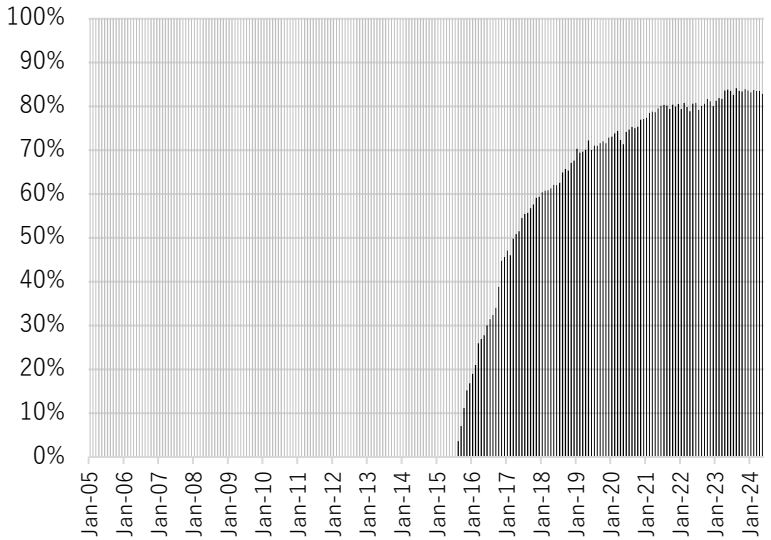


Figure 1

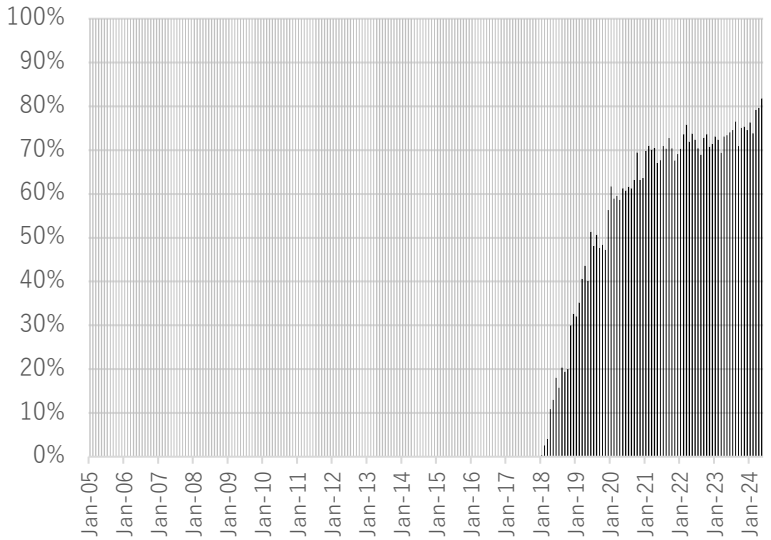
(5) Insulin glargine



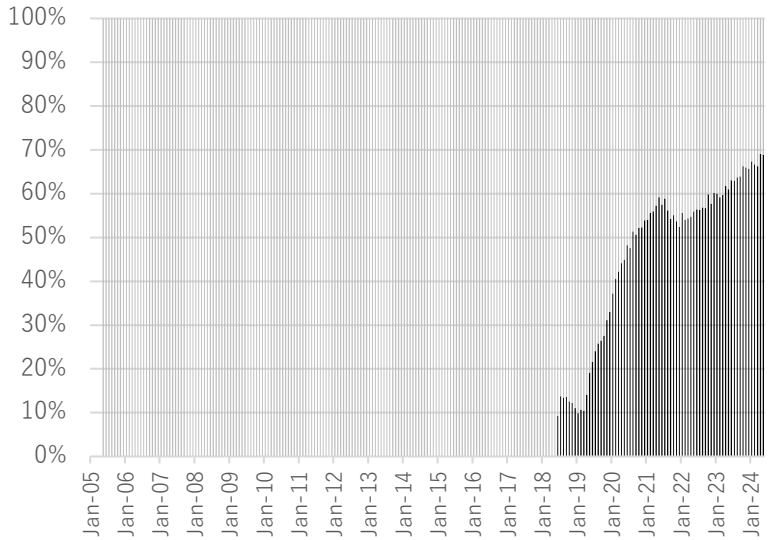
(5) Insulin glargine: sensitivity analysis



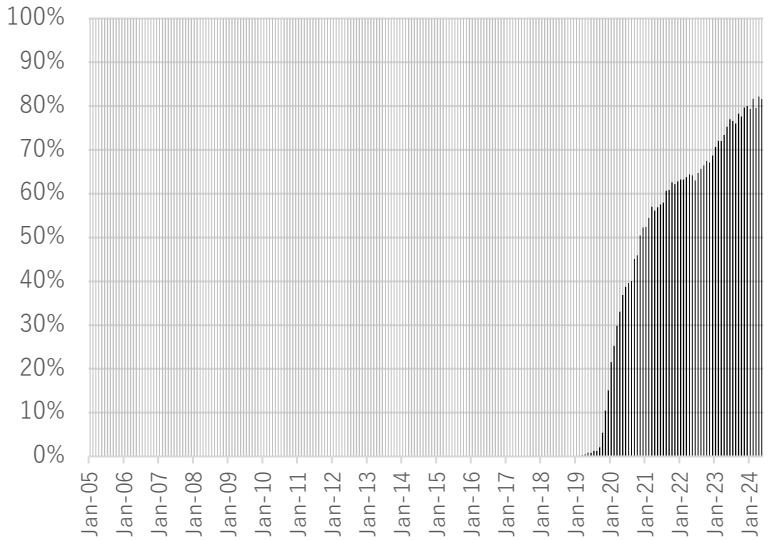
(6) Rituximab



(7) Etanercept



(8) Trastuzumab



(9) Agalsidase beta

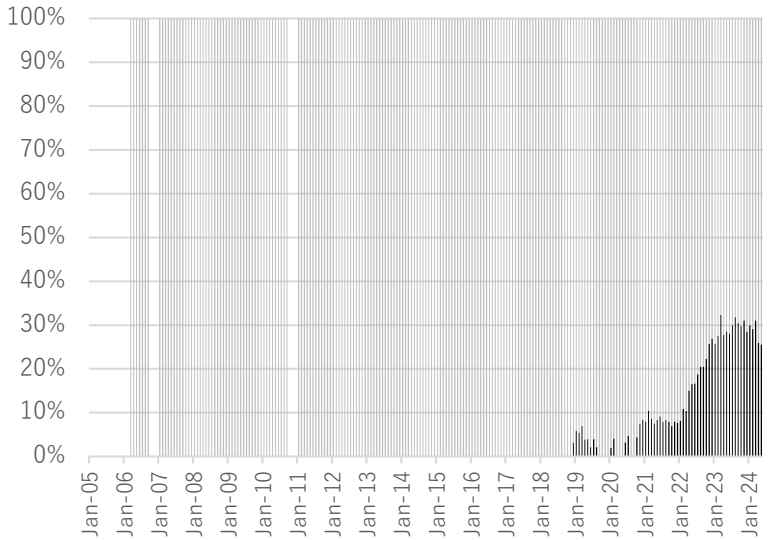
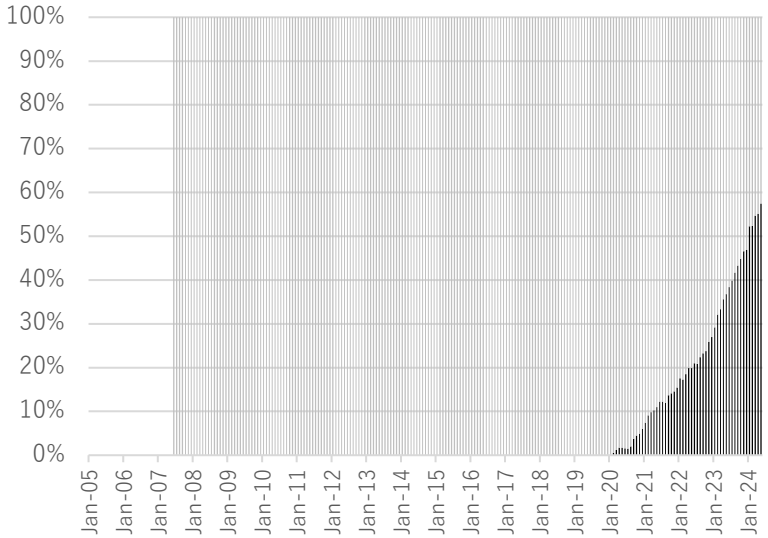
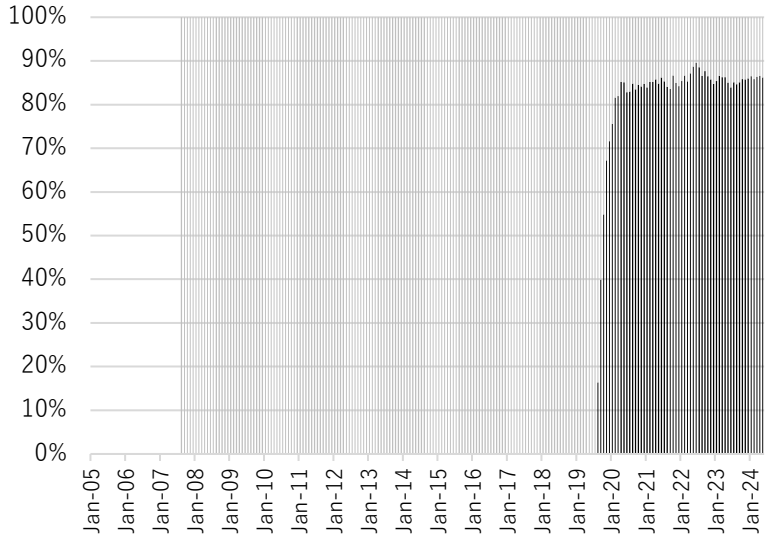


Figure 1

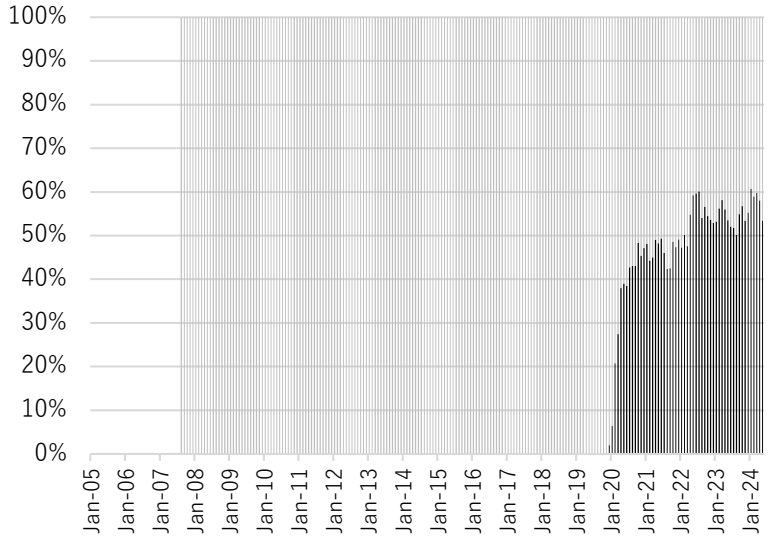
(10) Bevacizumab



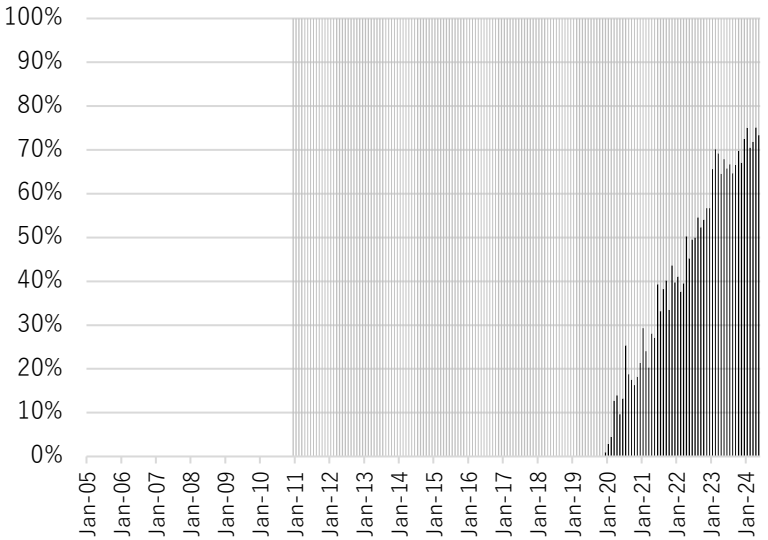
(11) Darbepoetin alfa



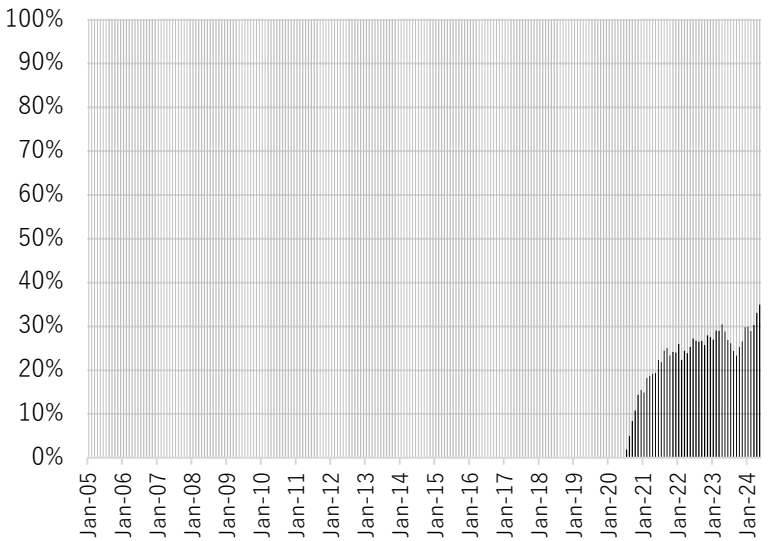
(11) Darbepoetin alfa: sensitivity analysis



(12) Teriparatide



(13) Insulin lispro



(13) Insulin lispro: sensitivity analysis

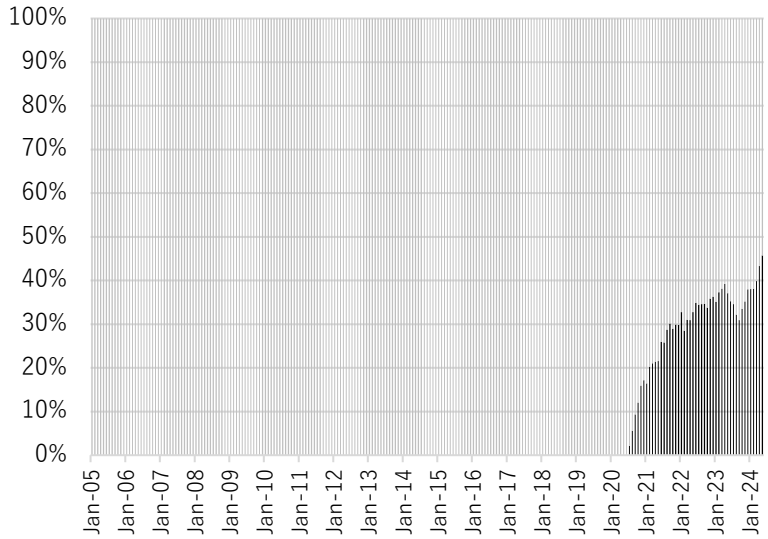
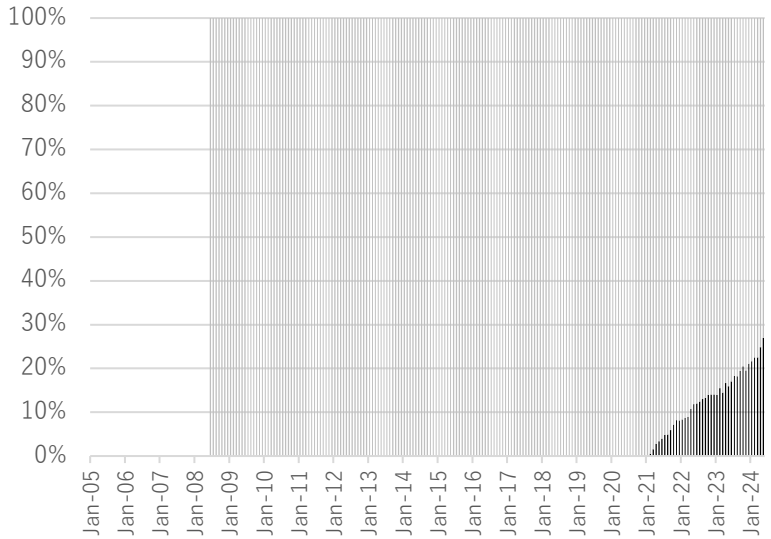
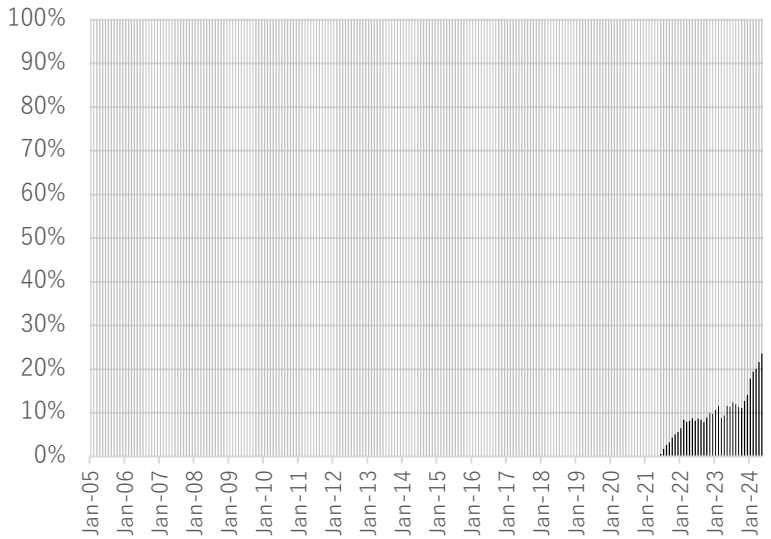


Figure 1

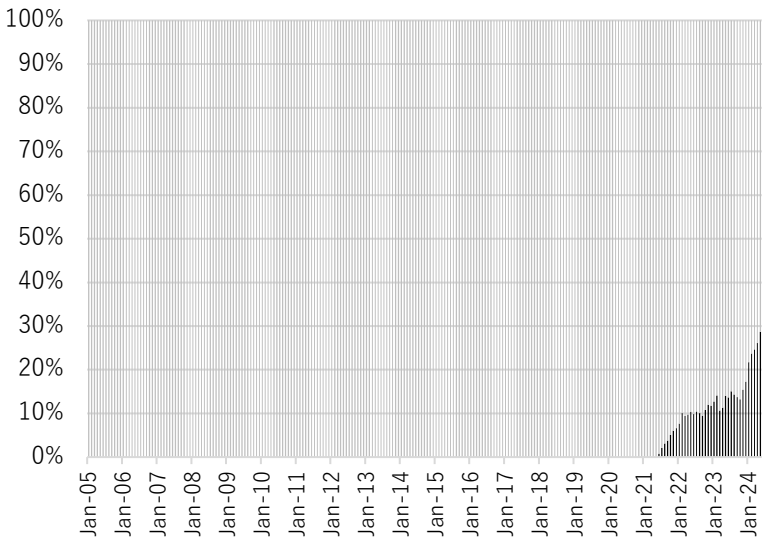
(14) Adalimumab



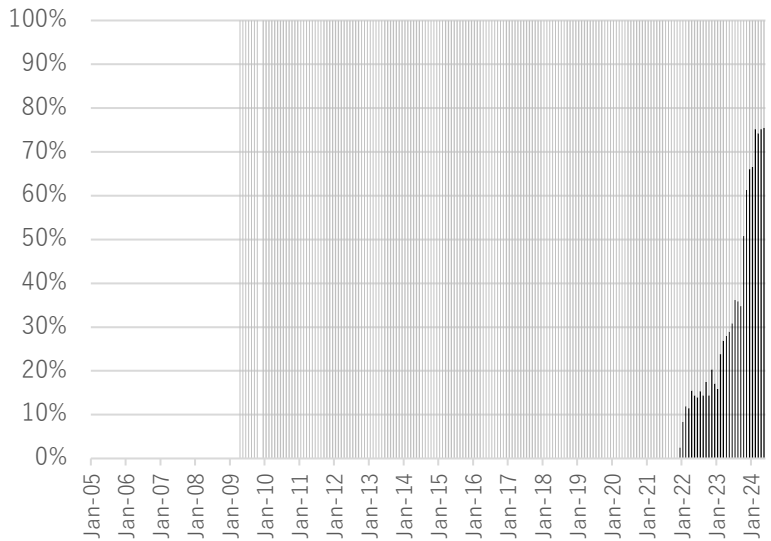
(15) Insulin aspart



(15) Insulin aspart: sensitivity analysis



(16) Ranibizumab



(17) Pegfilgrastim

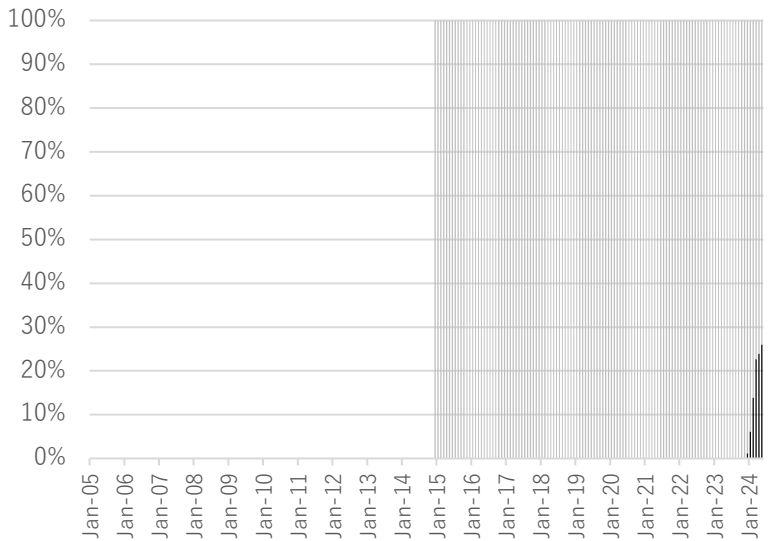


Figure 1

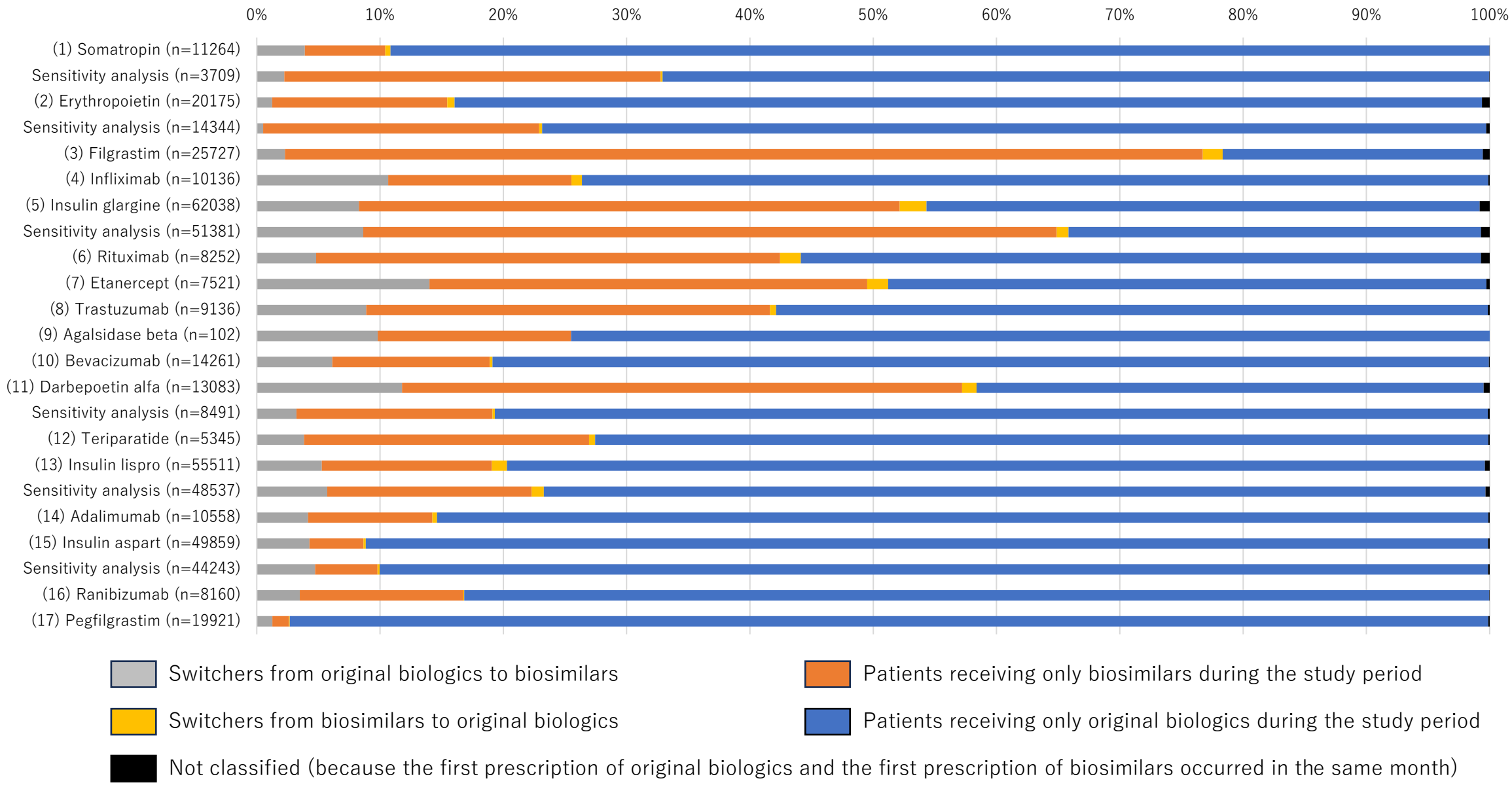

0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
(1) Somatropin (n=11264)
Sensitivity analysis (n=3709)
(2) Erythropoietin (n=20175)
Sensitivity analysis (n=14344)
(3) Filgrastim (n=25727)
(4) Infliximab (n=10136)
(5) Insulin glargine (n=62038)
Sensitivity analysis (n=51381)
(6) Rituximab (n=8252)
(7) Etanercept (n=7521)
(8) Trastuzumab (n=9136)
(9) Agalsidase beta (n=102)
(10) Bevacizumab (n=14261)
(11) Darbepoetin alfa (n=13083)
Sensitivity analysis (n=8491)
(12) Teriparatide (n=5345)
(13) Insulin lispro (n=55511)
Sensitivity analysis (n=48537)
(14) Adalimumab (n=10558)
(15) Insulin aspart (n=49859)
Sensitivity analysis (n=44243)
(16) Ranibizumab (n=8160)
(17) Pegfilgrastim (n=19921)
Switchers from original biologics to biosimilars
Patients receiving only biosimilars during the study period
Switchers from biosimilars to original biologics
Patients receiving only original biologics during the study period
Not classified (because the first prescription of original biologics and the first prescription of biosimilars occurred in the same month)

Figure 2

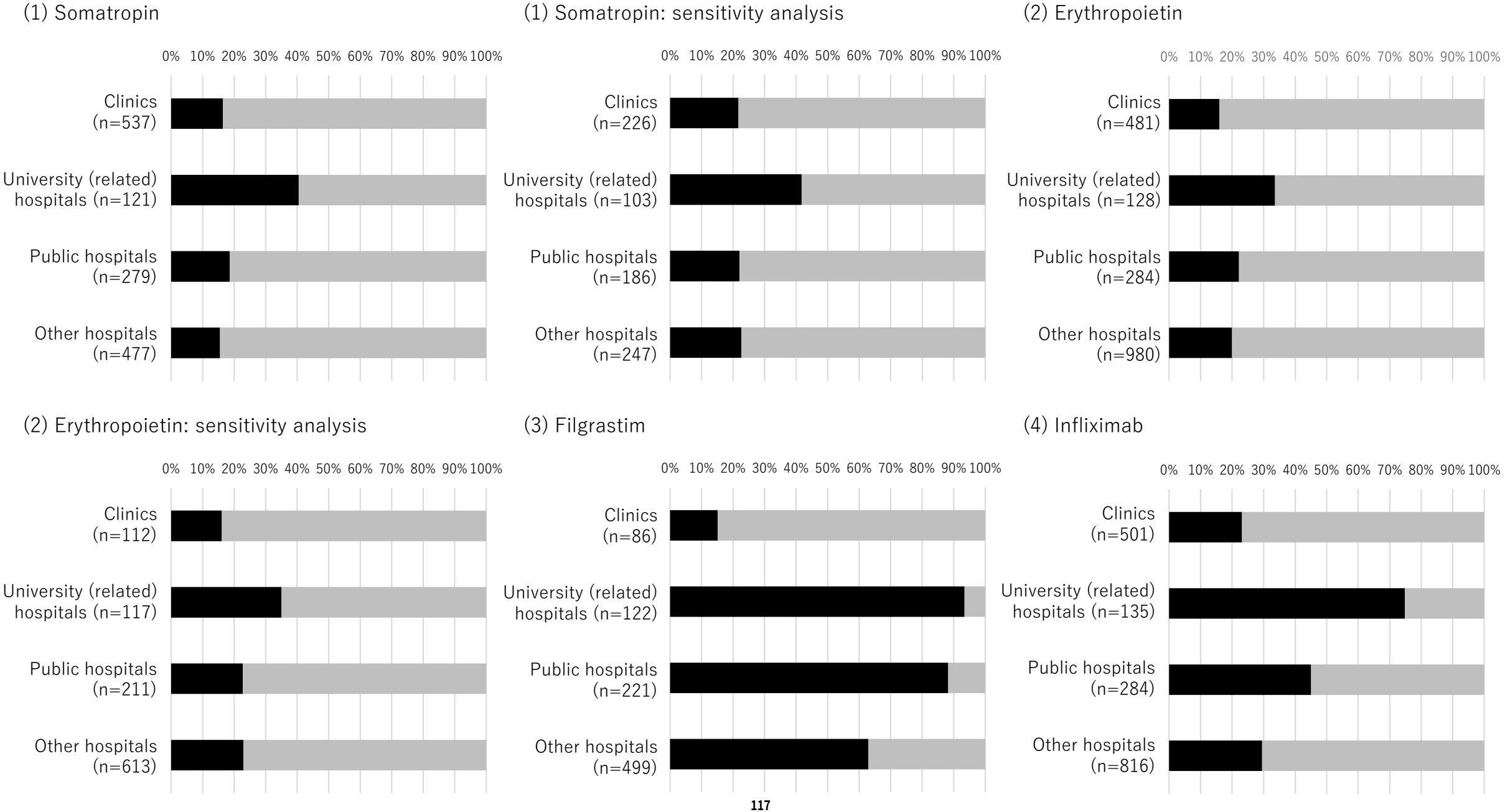

(1) Somatropin
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Clinics (n=537)
University (related) hospitals (n=121)
Public hospitals (n=279)
Other hospitals (n=477)
(1) Somatropin: sensitivity analysis
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Clinics (n=226)
University (related) hospitals (n=103)
Public hospitals (n=186)
Other hospitals (n=247)
(2) Erythropoietin
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Clinics (n=481)
University (related) hospitals (n=128)
Public hospitals (n=284)
Other hospitals (n=980)
(2) Erythropoietin: sensitivity analysis
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Clinics (n=112)
University (related) hospitals (n=117)
Public hospitals (n=211)
Other hospitals (n=613)
(3) Filgrastim
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Clinics (n=86)
University (related) hospitals (n=122)
Public hospitals (n=221)
Other hospitals (n=499)
(4) Infliximab
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Clinics (n=501)
University (related) hospitals (n=135)
Public hospitals (n=284)
Other hospitals (n=816)

Figure 3

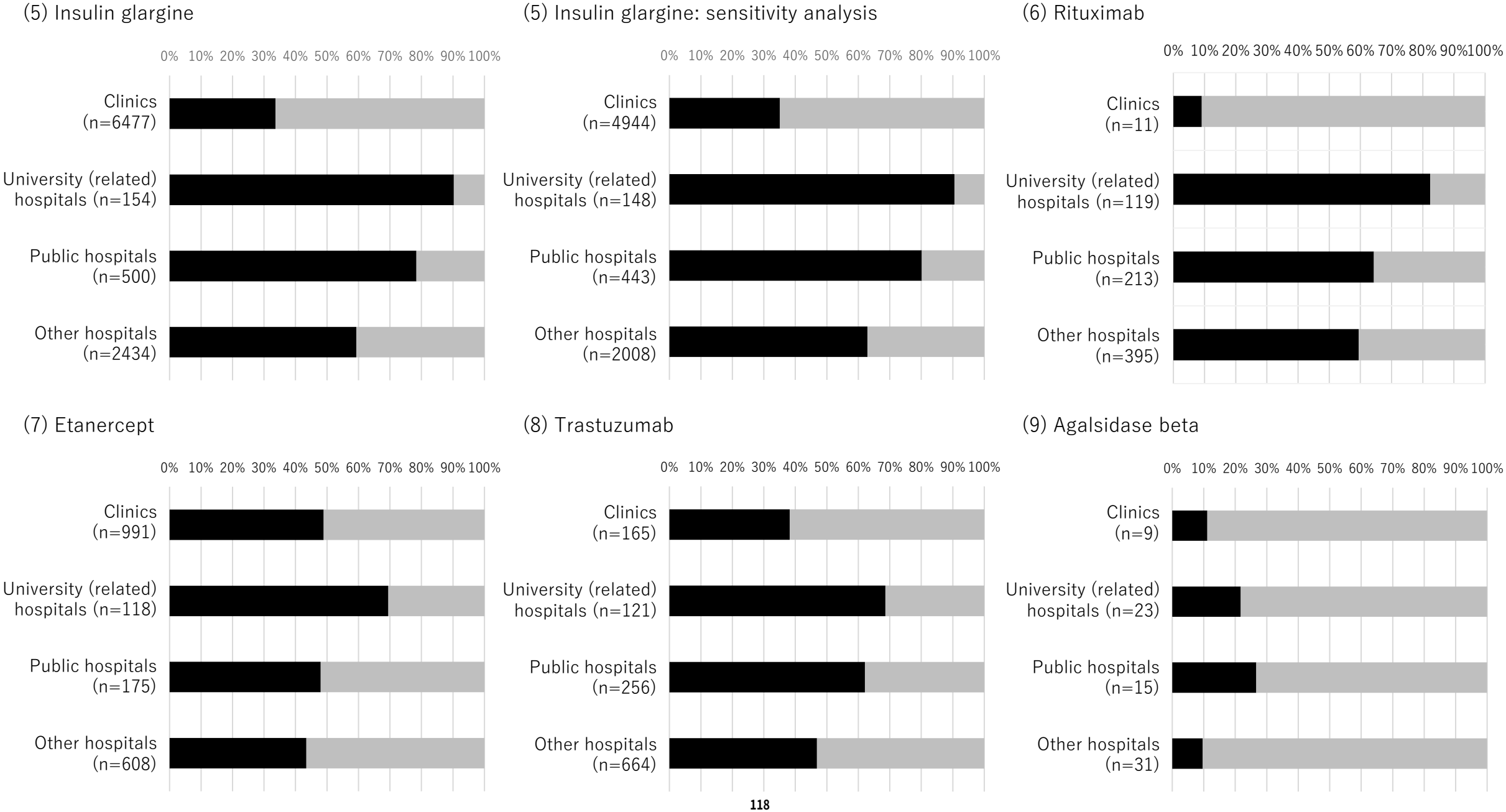

(5) Insulin glargine
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Clinics (n=6477)
University (related) hospitals (n=154)
Public hospitals (n=500)
Other hospitals (n=2434)
(5) Insulin glargine: sensitivity analysis
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Clinics (n=4944)
University (related) hospitals (n=148)
Public hospitals (n=443)
Other hospitals (n=2008)
(6) Rituximab
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Clinics (n=11)
University (related) hospitals (n=119)
Public hospitals (n=213)
Other hospitals (n=395)
(7) Etanercept
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Clinics (n=991)
University (related) hospitals (n=118)
Public hospitals (n=175)
Other hospitals (n=608)
(8) Trastuzumab
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Clinics (n=165)
University (related) hospitals (n=121)
Public hospitals (n=256)
Other hospitals (n=664)
(9) Agalsidase beta
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Clinics (n=9)
University (related) hospitals (n=23)
Public hospitals (n=15)
Other hospitals (n=31)

Figure 3

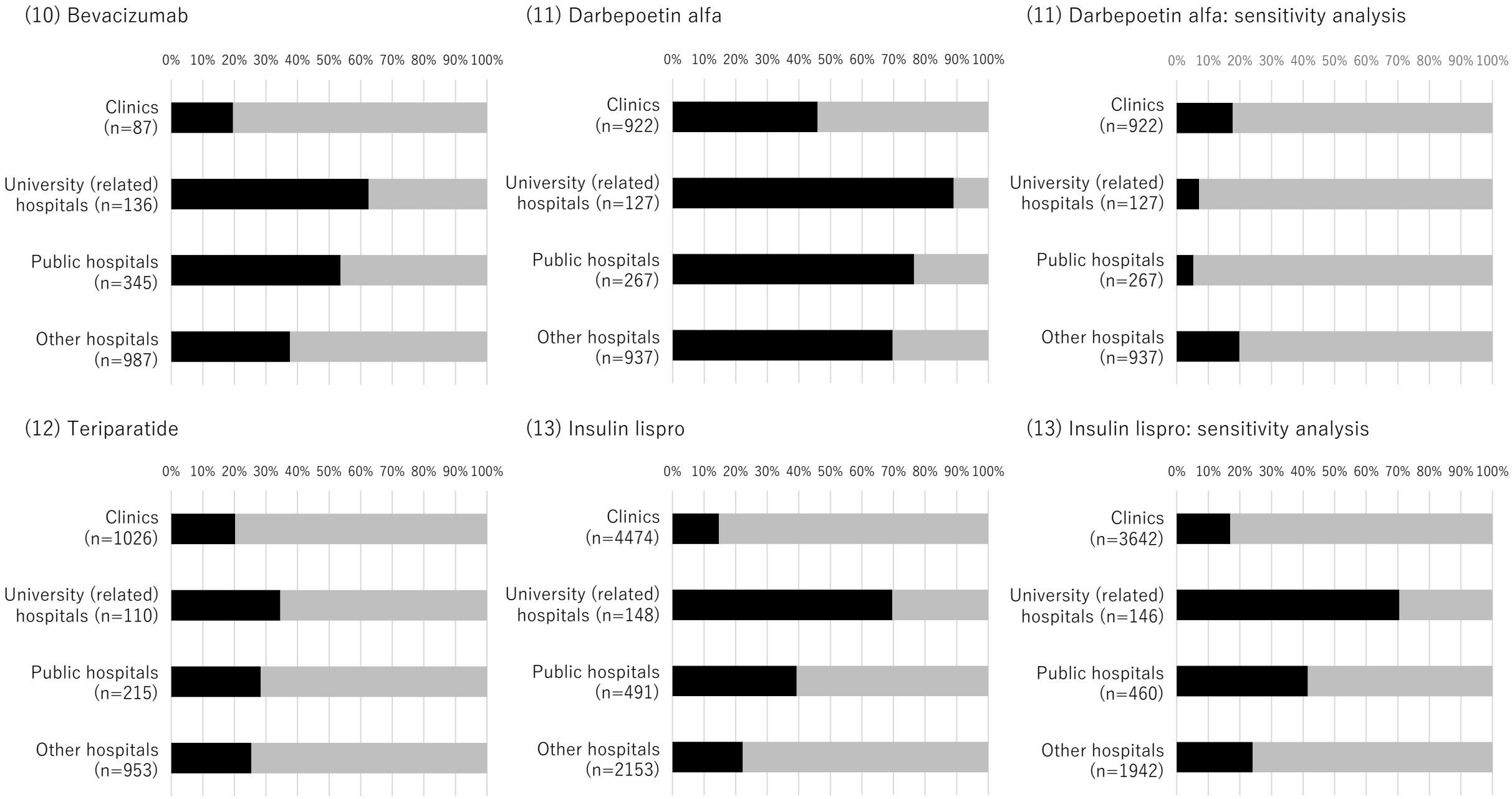
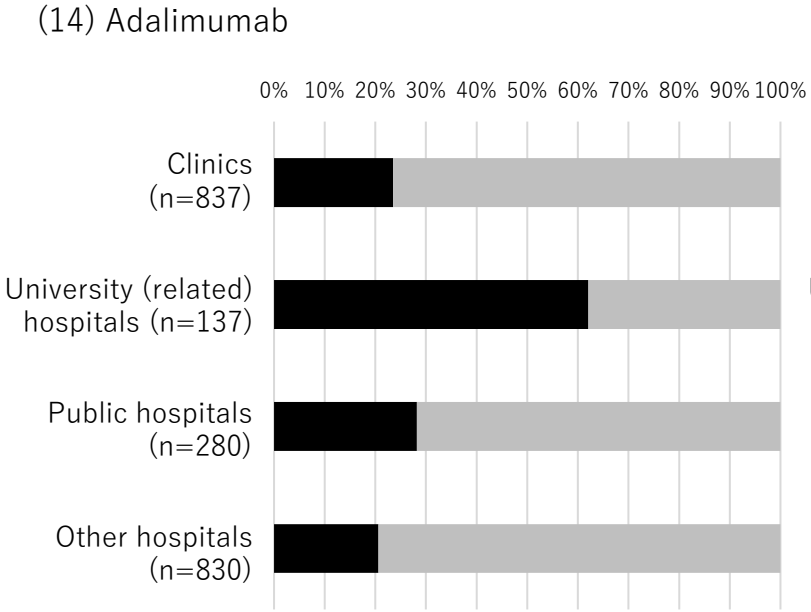
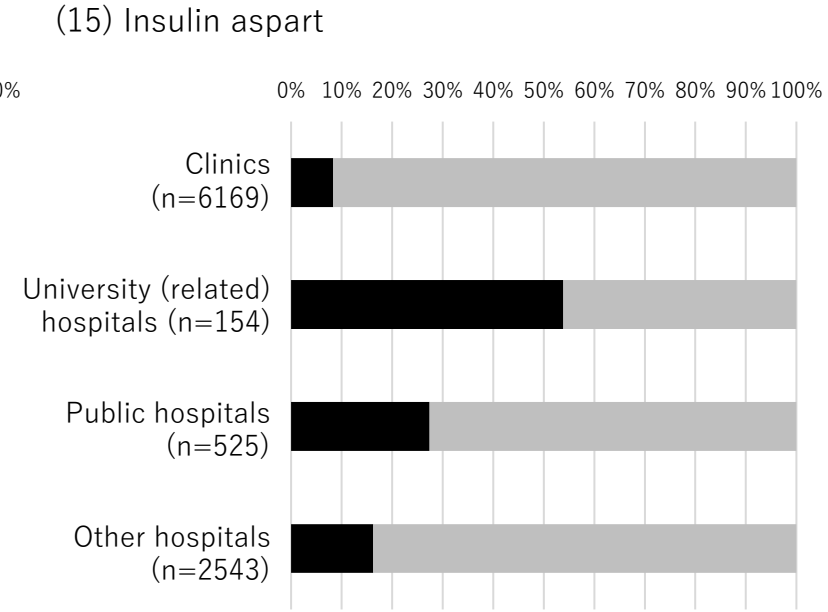
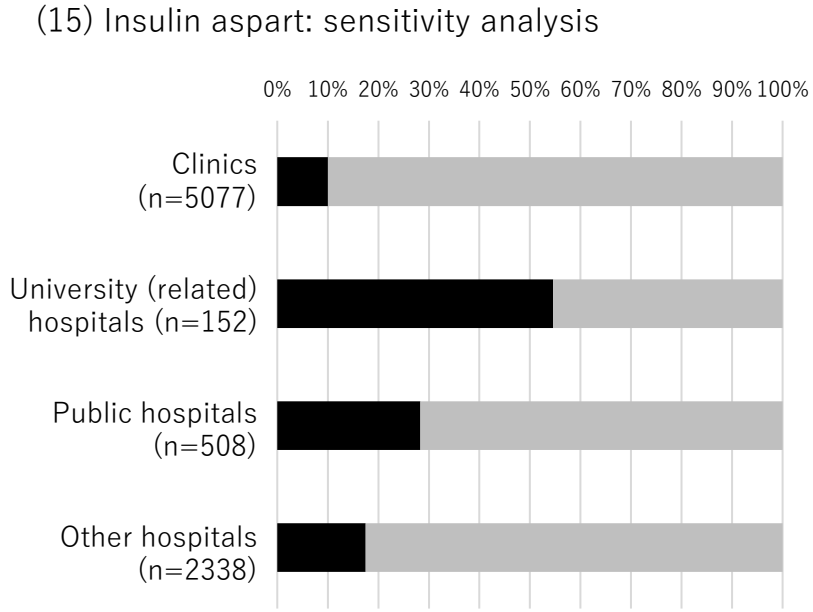
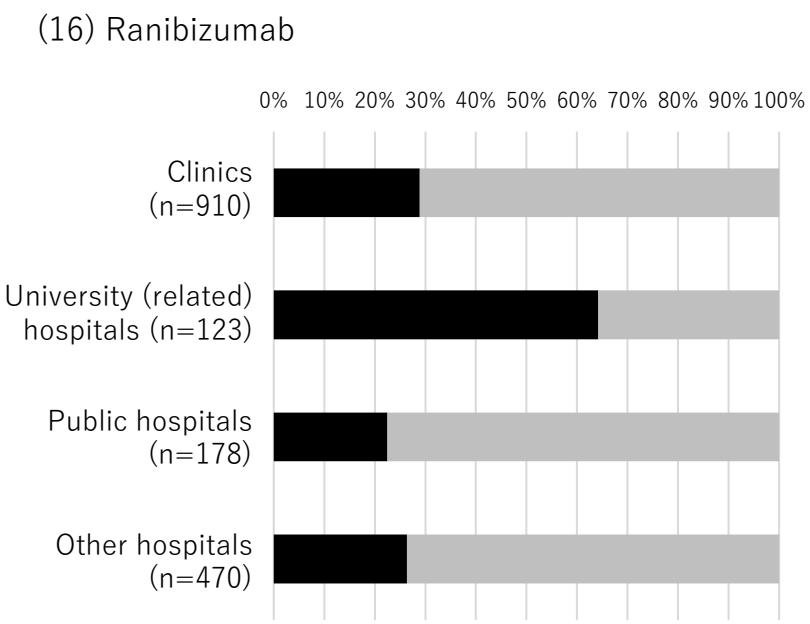

(10) Bevacizumab
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Clinics (n=87)
University (related) hospitals (n=136)
Public hospitals (n=345)
Other hospitals (n=987)
(11) Darbepoetin alfa
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Clinics (n=922)
University (related) hospitals (n=127)
Public hospitals (n=267)
Other hospitals (n=937)
(11) Darbepoetin alfa: sensitivity analysis
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Clinics (n=922)
University (related) hospitals (n=127)
Public hospitals (n=267)
Other hospitals (n=937)
(12) Teriparatide
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Clinics (n=1026)
University (related) hospitals (n=110)
Public hospitals (n=215)
Other hospitals (n=953)
(13) Insulin lispro
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Clinics (n=4474)
University (related) hospitals (n=148)
Public hospitals (n=491)
Other hospitals (n=2153)
(13) Insulin lispro: sensitivity analysis
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Clinics (n=3642)
University (related) hospitals (n=146)
Public hospitals (n=460)
Other hospitals (n=1942)

Figure 3


(14) Adalimumab
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Clinics (n=837)
University (related) hospitals (n=137)
Public hospitals (n=280)
Other hospitals (n=830)


(15) Insulin aspart
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Clinics (n=6169)
University (related) hospitals (n=154)
Public hospitals (n=525)
Other hospitals (n=2543)


(15) Insulin aspart: sensitivity analysis
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Clinics (n=5077)
University (related) hospitals (n=152)
Public hospitals (n=508)
Other hospitals (n=2338)


(16) Ranibizumab
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Clinics (n=910)
University (related) hospitals (n=123)
Public hospitals (n=178)
Other hospitals (n=470)

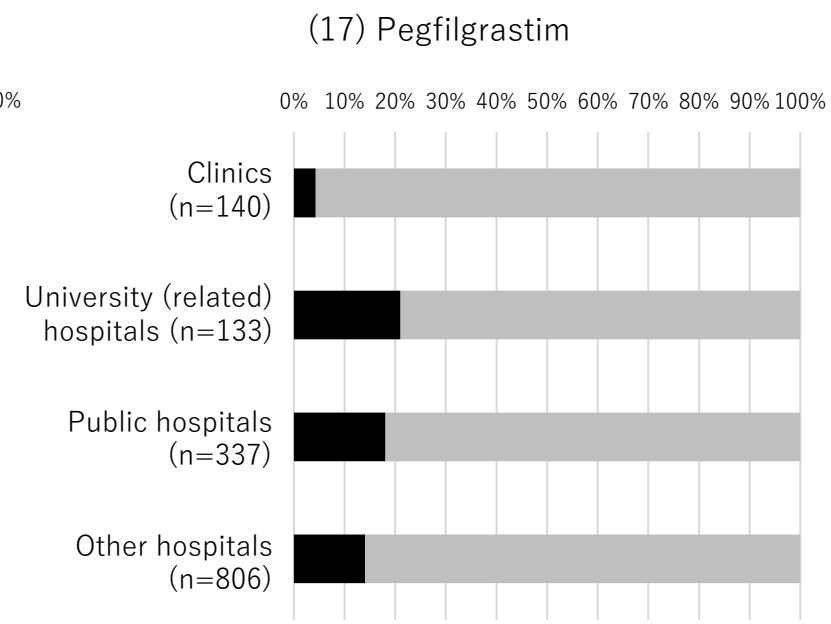

(17) Pegfilgrastim
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Clinics (n=140)
University (related) hospitals (n=133)
Public hospitals (n=337)
Other hospitals (n=806)

Figure 3

Supplementary Table S1. List of product names and classifications

Name	ATC code	Original biologic	Biosimilar
1. Somatropin	H01AC01	Genotropin*	Somatropin BS
		Growject	–
		Saizen	–
		Norditropin	–
		Humatrope	–
2. Erythropoietin***	B03XA01	Espo*	Epoetin Alfa BS (Epoetin Kappa)
		Epogin	
3. Filgrastim	L03AA02	Gran*	Filgrastim BS
4. Infliximab	L04AB02	Remicade*	Infliximab BS
5. Insulin glargine	A10AE04	Lantus*	Insulin Glargine BS
		Lantus XR	–
6. Rituximab	L01FA01	Rituxan*	Rituximab BS
7. Etanercept	L04AB01	Enbrel*	Etanercept BS
8. Trastuzumab	L01FD01	Herceptin*	Trastuzumab BS
9. Agalsidase beta	A16AB04	Fabrazyme*	Agalsidase Beta BS
10. Bevacizumab	L01FG01	Avastin*	Bevacizumab BS
11. Darbepoetin alfa	B03XA02	Nesp*	Darbepoetin Alfa BS
			Darbepoetin Alfa**
12. Teriparatide	H05AA02	Forteo*	Teriparatide BS
13. Insulin lispro	A10AB04 A10AC04 A10AD04	Humalog*	Insulin Lispro BS
		Humalog Mix	–
		Humalog N	–
		Lyumjev	–
14. Adalimumab	L04AB04	Humira*	Adalimumab BS
15. Insulin aspart	A10AB05 A10AD05	NovoRapid*	Insulin Aspart BS
		NovoRapid Mix	–
		Fiasp	–
16. Ranibizumab	S01LA04	Lucentis*	Ranibizumab BS
17. Pegfilgrastim	L03AA13	G-lasta*	Pegfilgrastim BS

* Reference product of biosimilar.

** Authorized generic (AG) biologic drug.

***Different from other biologics, “Erythropoietin” is not a generic name but used here because multiple active ingredients exist for original biologics, including epoetin alfa (Espo) and epoetin beta (Epogin).

Supplementary Table S2. Comparison of number of prescriptions and propotion of biosimilars between the JMDC claims database and the NDB Open Data from April 2022 to March 2023

Name	JMDC claims database from April 2022 to March 2023		NDB Open Data from April 2022 to March 2023	
	Total no. of prescriptions for both original biologics and biosimilars	No. of prescriptions for biosimilars (%)	Total no. of prescriptions for both original biologics and biosimilars	Total no. of prescriptions for both original biologics and biosimilars
(1) Somatropin	34,931	2,859 (8.2)	1087,245	84,386 (7.8)
Sensitivity analysis*	8,943	2,859 (32.0)	285,465	84,386 (29.6)
(2) Erythropoietin	16,083	5,278 (32.8)	337,188	121,294 (36.0)
Sensitivity analysis*	12,140	5,278 (43.5)	186,132	121,294 (65.2)
(3) Filgrastim	39,343	36,552 (92.9)	907,989	861,176 (94.8)
(4) Infliximab	25,590	7,349 (28.7)	937,777	272,924 (29.1)
(5) Insulin glargine	162,849	91,755 (56.3)	6070,213	3267,121 (53.8)
Sensitivity analysis*	113,707	91,755 (80.7)	4446,768	3267,121 (73.5)
(6) Rituximab	11,134	7,986 (71.7)	357,789	282,047 (78.8)
(7) Etanercept	23,607	13,654 (57.8)	1925,756	898,041 (46.6)
(8) Trastuzumab	29,597	19,915 (67.3)	918,232	602,321 (65.6)
(9) Agalsidase beta	1,808	411 (22.7)	45,713	8,063 (17.6)
(10) Bevacizumab	37,689	9,426 (25.0)	1577,373	425,443 (27.0)
(11) Darbepoetin alfa	14,436	12,550 (86.9)	1518,781	1198,118 (78.9)
Sensitivity analysis*	4,293	2,407 (56.1)	522,992	201,751 (38.6)
(12) Teriparatide	9,071	5,082 (56.0)	754,299	329,326 (43.7)
(13) Insulin lispro	156,459	42,161 (26.9)	9079,238	1824,060 (20.1)
Sensitivity analysis*	120,711	42,161 (34.9)	6552,217	1824,060 (27.8)
(14) Adalimumab	29,496	3,926 (13.3)	1090,901	136,087 (12.5)
(15) Insulin aspart	132,168	12,139 (9.2)	8663,964	535,289 (6.2)
Sensitivity analysis*	110,409	12,139 (11.0)	6693,072	535,289 (8.0)
(16) Ranibizumab	3,464	603 (17.4)	168,422	26,819 (15.9)
(17) Pegfilgrastim	16,297	0 (0.0)	306,436	0 (0.0)

NDB, National Database.

*While all the original biologics or biosimilars available in Japan were included in the main analysis, the sensitivity analysis made the changes below (corresponding to Supplementary Table S1):

- For somatropin, we considered Genotropin vs. Somatropin BS.
- For erythropoietin, we considered Espo vs. Epoetin Alfa BS (Epoetin Kappa).
- For insulin glargine, we considered Lantus (not including Lantus XR) vs. Insulin Glargine BS.
- For darbepoetin alfa, we considered Nesp vs. Darbepoetin Alfa BS (not including Darbepoetin Alfa authorized generic).
- For insulin lispro, we considered Humalog (not including Humalog Mix and Humalog N) vs. Insulin Lispro BS.
- For insulin aspart, we considered NovoRapid (not including NovoRapid Mix) vs. Insulin Aspart BS.

Supplementary Table S3. Distribution of patients using only original biologics or biosimilars or switchers during the study period

Drug	Main analysis from Jan, 2005 to May, 2024						Additional analysis restricting to patients using drugs only during the period from when each biosimilar was approved to May, 2024						
	Switchers from original biologics to biosimilars	Patients using only biosimilars	Switchers from biosimilars to original biologics	Patients using only original biologics	Not classified*	Total no. of patients	When each biosimilar was approved	Switchers from original biologics to biosimilars	Patients using only biosimilars	Switchers from biosimilars to original biologics	Patients using only original biologics	Not classified*	Total no. of patients
(1) Somatropin	440 (3.9%)	734 (6.5%)	47 (0.4%)	10,042 (89.2%)	1 (<0.1%)	11,264 (100%)	Jun, 2009	439 (4.0%)	734 (6.6%)	47 (0.4%)	9,835 (89.0%)	1 (<0.1%)	11,056 (100%)
Sensitivity analysis**	83 (2.2%)	1,132 (30.5%)	6 (0.2%)	2,487 (67.1%)	1 (<0.1%)	3,709 (100%)		82 (2.3%)	1,132 (31.2%)	6 (0.2%)	2,404 (66.3%)	1 (<0.1%)	3,625 (100%)
(2) Erythropoietin	252 (1.2%)	2,864 (14.2%)	122 (0.6%)	16,812 (83.3%)	125 (0.6%)	20,175 (100%)	Jan, 2010	234 (1.2%)	2,864 (14.7%)	122 (0.6%)	16,102 (82.8%)	125 (0.6%)	19,447 (100%)
Sensitivity analysis**	74 (0.5%)	3,211 (22.4%)	36 (0.3%)	10,981 (76.6%)	42 (0.3%)	14,344 (100%)		68 (0.5%)	3,211 (23.2%)	36 (0.3%)	10,509 (75.8%)	42 (0.3%)	13,866 (100%)
(3) Filgrastim	590 (2.3%)	19,151 (74.4%)	415 (1.6%)	5,427 (21.1%)	144 (0.6%)	25,727 (100%)	Nov, 2012	558 (2.3%)	19,151 (78.5%)	415 (1.7%)	4,129 (16.9%)	144 (0.6%)	24,397 (100%)
(4) Infliximab	1,080 (10.7%)	1,507 (14.9%)	86 (0.8%)	7,451 (73.5%)	12 (0.1%)	10,136 (100%)	Jul, 2014	918 (10.7%)	1,507 (17.5%)	86 (1.0%)	6,090 (70.7%)	12 (0.1%)	8,613 (100%)
(5) Insulin glargine	5,142 (8.3%)	27,208 (43.9%)	1,350 (2.2%)	27,838 (44.9%)	500 (0.8%)	62,038 (100%)	Dec, 2014	3,603 (6.7%)	27,208 (50.4%)	1,350 (2.5%)	21,361 (39.5%)	500 (0.9%)	54,022 (100%)
Sensitivity analysis**	4,440 (8.6%)	28,903 (56.3%)	489 (1.0%)	17,181 (33.4%)	368 (0.7%)	51,381 (100%)		2,901 (6.7%)	28,903 (66.7%)	489 (1.1%)	10,704 (24.7%)	368 (0.9%)	43,365 (100%)
(6) Rituximab	398 (4.8%)	3,105 (37.6%)	138 (1.7%)	4,552 (55.2%)	59 (0.7%)	8,252 (100%)	Sep, 2017	279 (4.5%)	3,105 (49.5%)	138 (2.2%)	2,693 (42.9%)	59 (0.9%)	6,274 (100%)
(7) Etanercept	1,053 (14.0%)	2,671 (35.5%)	128 (1.7%)	3,649 (48.5%)	20 (0.3%)	7,521 (100%)	Jan, 2018	529 (10.5%)	2,671 (53.0%)	128 (2.5%)	1,695 (33.6%)	20 (0.4%)	5,043 (100%)

(8) Trastuzumab	811 (8.9%)	2,992 (32.7%)	45 (0.5%)	5,275 (57.7%)	13 (0.1%)	9,136 (100%)	Mar, 2018	687 (11.1%)	2,992 (48.3%)	45 (0.7%)	2,463 (39.7%)	13 (0.2%)	6,200 (100%)
(9) Agalsidase beta	10 (9.8%)	16 (15.7%)	0 (0%)	76 (74.5%)	0 (0%)	102 (100%)	Sep, 2018	4 (5.7%)	16 (22.9%)	0 (0%)	50 (71.4%)	0 (0%)	70 (100%)
(10) Bevacizumab	873 (6.1%)	1,823 (12.8%)	31 (0.2%)	11,525 (80.8%)	9 (0.1%)	14,261 (100%)	Jun, 2019	747 (8.8%)	1,823 (21.5%)	31 (0.4%)	5,881 (69.3%)	9 (0.1%)	8,491 (100%)
(11) Darbepoetin alfa	1,542 (11.8%)	5,942 (45.4%)	153 (1.2%)	5,382 (41.1%)	64 (0.5%)	13,083 (100%)	Sep, 2019	216 (3.1%)	5,927 (85.8%)	153 (2.2%)	557 (8.1%)	57 (0.8%)	6,910 (100%)
Sensitivity analysis**	273 (3.2%)	1,350 (5.9%)	16 (0.2%)	6,839 (80.5%)	13 (0.2%)	8,491 (100%)		65 (2.8%)	1,350 (57.9%)	16 (0.7%)	889 (38.1%)	13 (0.6%)	2,333 (100%)
(12) Teriparatide	205 (3.8%)	1,236 (23.1%)	26 (0.5%)	3,872 (72.4%)	6 (0.1%)	5,345 (100%)	Sep, 2019	162 (5.9%)	1,236 (45.1%)	26 (1.0%)	1,311 (47.8%)	6 (0.2%)	2,741 (100%)
(13) Insulin lispro	2,924 (5.3%)	7,663 (13.8%)	679 (1.2%)	44,033 (79.3%)	212 (0.4%)	55,511 (100%)	Mar, 2020	1,099 (3.7%)	7,663 (26.0%)	679 (2.3%)	19,817 (67.2%)	212 (0.7%)	29,470 (100%)
Sensitivity analysis**	2,780 (5.7%)	8,052 (16.6%)	483 (1.0%)	37,059 (76.4%)	163 (0.3%)	48,537 (100%)		1,021 (4.0%)	8,052 (31.5%)	483 (1.9%)	15,875 (62.0%)	163 (0.6%)	25,594 (100%)
(14) Adalimumab	438 (4.2%)	1,066 (10.1%)	40 (0.4%)	9,002 (85.3%)	12 (0.1%)	10,558 (100%)	Jun, 2020	219 (4.2%)	1,066 (20.6%)	40 (0.8%)	3,845 (74.2%)	12 (0.2%)	5,182 (100%)
(15) Insulin aspart	2,132 (4.3%)	2,182 (4.4%)	91 (0.2%)	45,392 (91.0%)	62 (0.1%)	49,859 (100%)	Mar, 2021	769 (4.6%)	2,182 (13.1%)	91 (0.6%)	13,561 (81.4%)	62 (0.4%)	16,665 (100%)
Sensitivity analysis**	2,090 (4.7%)	2,241 (5.1%)	81 (0.2%)	39,776 (89.9%)	55 (0.1%)	44,243 (100%)		758 (5.1%)	2,241 (15.0%)	81 (0.5%)	11,837 (79.1%)	55 (0.4%)	14,972 (100%)
(16) Ranibizumab	285 (3.5%)	1,083 (13.3%)	5 (0.1%)	6,784 (83.1%)	3 (<0.1%)	8,160 (100%)	Sep, 2021	182 (6.0%)	1,083 (35.5%)	5 (0.2%)	1,780 (58.3%)	3 (0.1%)	3,053 (100%)
(17) Pegfilgrastim	252 (1.3%)	269 (1.4%)	13 (0.1%)	19,365 (97.2%)	22 (0.1%)	19,921 (100%)	Sep, 2023	172 (6.7%)	269 (10.5%)	13 (0.5%)	2,090 (81.5%)	22 (0.9%)	2,566 (100%)

Note: For switchers, only the first switch was assessed and counted (i.e., there were some patients who switched twice or more times)

*The first prescription of original biologics and the first prescription of biosimilars occurred in the same month, so that the researchers could not differentiate which was started first.

**While all the original biologics or biosimilars available in Japan were included in the main analysis, the sensitivity analysis made the changes below (corresponding to Supplementary Table S1):

- For somatropin, we considered Genotropin vs. Somatropin BS.
- For erythropoietin, we considered Espo vs. Epoetin Alfa BS (Epoetin Kappa).
- For insulin glargine, we considered Lantus (not including Lantus XR) vs. Insulin Glargine BS.
- For darbepoetin alfa, we considered Nesp vs. Darbepoetin Alfa BS (not including Darbepoetin Alfa authorized generic).
- For insulin lispro, we considered Humalog (not including Humalog Mix and Humalog N) vs. Insulin Lispro BS.
- For insulin aspart, we considered NovoRapid (not including NovoRapid Mix) vs. Insulin Aspart BS.