Budget Impact Analysis of Trastuzumab Biosimilar for the Treatment of Breast Cancer and Gastric Cancer in China

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Abstract

Background: Breast cancer and gastric cancer are the two major cancers in terms of incidence among all malignancies in China. Trastuzumab is a high-priced antitumor targeted drug indicated for the treatment of human epidermal growth factor receptor 2 (HER2)-positive early breast cancer (EBC), metastatic breast cancer (MBC) and metastatic gastric cancer (MGC). Trastuzumab, as a price negotiation, was added to the National Reimbursement Medicine List (NRML) in China in 2017 and was the drug with the highest financial consumption among all cancer drugs in 2018. A trastuzumab biosimilar gained market authorization in China in August 2020. This study aimed to estimate the budgetary impact of switching from a trastuzumab originator to a trastuzumab biosimilar from the Chinese payer's perspective and the number of additional patients who could be treated with the biosimilar as resulting savings in China.

Methods: Five-year budgetary savings and the number of patients potentially affected were measured based on epidemiological data of breast and gastric cancers in the Chinese population available in the literature, trastuzumab market projected data in China, and original and biosimilar drug doses and costs. The robustness of the model was tested with extensive sensitivity analyses.

Results: The projected budgetary savings ranged from 0.59-1.03 billion RMB over a 5-year time period, and the total cost of savings was 3.97 billion RMB. The number of additional patients who could be treated with the biosimilar according to the budget savings would be 9005-15762. Most cost savings refer to the treatment of HER2-positive EBC (86%). Sensitivity analyses showed that the prices of the trastuzumab originator and biosimilar and the number of patients treated with trastuzumab were major influencing factors.

Conclusions: The introduction and penetration of a trastuzumab biosimilar in China could lead to significant budget savings. Further studies could focus on improving the refined management of drug prescriptions, particularly for HER2-positive EBC, and therefore improve the efficiency of drug costs.

Key Points

- China is a large population, and the incidences of breast cancer and gastric cancer are among the highest in the world.
- The introduction and penetration of a trastuzumab biosimilar into China and switching from a trastuzumab originator to a trastuzumab biosimilar would greatly reduce healthcare expenditures from the Chinese payer's perspective.
- The potential result of cost savings from switching to the biosimilar could greatly promote better access to biological therapy for patients with trastuzumab indications, improve patient outcomes, and benefit more people.

Background

Cancer incidence and mortality have been increasing, making cancer the leading cause of death since 2010 and a major public health problem in China. China ranks first in the world in cancer incidence based on global cancer statistics in 2018 and 2020 [1, 2]. Among many cancers, breast cancer ranks first among female cancers; its incidence rate is increasing year by year. The rate of increase in the incidence of breast cancer in China is more than twice the global rate and starts in young women. Gastric cancer is the second most common cancer in terms of incidence among all malignancies in China [3, 4]. The number of incident cases of gastric cancer in China accounts for 42.6% of the global incidence and 45% of all gastric cancer-related deaths [5, 6].

Cancer patients with human epidermal growth factor receptor 2 (HER2) overexpression have aggressive disease [7–9]. In China, 20–25% of breast cancer [7, 10] and 12–13% of gastric cancer [9, 11–13] patients are HER2 positive. Trastuzumab (Herceptin®; Roche), first approved for market authorization in the United States in 1998 and approved for import into Chinese in 2002, is a molecular targeted drug that inhibits tumor cell proliferation by binding to HER2 and is a currently approved indication for the treatment of patients with HER2-positive early breast cancer (EBC), HER2-positive metastatic breast cancer (MBC) and HER2-positive metastatic gastric cancer (MGC) in China [14, 15]. Numerous clinical studies have confirmed the clinical effectiveness and safety of trastuzumab for the treatment of HER2-positive breast cancer [16–23] and HER2-positive MBC [24]. Trastuzumab has been recommended as the standard treatment for HER2-positive postoperative breast cancer patients based on the Chinese National Comprehensive Cancer Network (NCCN) clinical practice guidelines for breast cancer. For the treatment of patients with HER2-positive MBC, trastuzumab combination therapy has been considered the standard first-line treatment [25]. In 2017, as a price negotiation, trastuzumab was placed into catalog B of the Medicine List for National Basic Medical Insurance, Employment Injury Insurance and Maternity Insurance (referred to as the National Reimbursement Medicine List, NRML). It was the drug with the highest financial consumption, reaching ¥2.7 billion (RMB) among all cancer drugs in China in 2018.

Biosimilar drugs are highly similar to licensed biologics based on the totality of evidence and show no clinically meaningful differences in quality attributes, safety, or efficacy compared with the reference drugs [26–29]. As biosimilar drugs are often offered at lower acquisition costs than originator drugs, their usage usually reduces the per-patient treatment cost, creates more access among patients and has a

substantial impact on the healthcare budget [30]. Thus, evaluation of the economic implications of switching to biosimilars is of interest. In August 2020, during the writing of this article, a China-manufactured trastuzumab biosimilar, HLX-02 (European Union Trade name: Zercepac® Henlius, Inc.), was approved by the National Medical Products Administration (NMPA). The biosimilar was approved for the same indications as its reference trastuzumab originator in China. Switching from the trastuzumab originator to the biosimilar may improve access to anti-HER2 therapies by providing additional treatment options and lower-cost alternatives and cause a substantial influence on the healthcare budget.

In this study, we developed a model to estimate a 5-year budget impact of interchangeability and substitution between the trastuzumab originator and biosimilar from the Chinese payer's perspective and estimated the number of additional patients who could be treated with the biosimilar as resulting savings in China. The model based on approval for trastuzumab covered the national medical insurance system in 2020 as a reference scenario. A biosimilar scenario was developed based on both the trastuzumab originator and biosimilar inclusion medical health care in 2021. The robustness of the model was tested by extensive sensitivity analyses.

Methods

A budget impact model was developed based on the recommendations of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force reported on "Budget Impact Analysis (BIA)—Principles of Good Practice" [31]. The model, with 2020 as the baseline year, in terms of the Chinese payer's perspective, projected the financial impact of switching from the originator to the biosimilar for the treatment of patients with HER2-positive EBC, MBC, and MGC over a 5-year time period (2021–2025) in China.

The model assumed the reference scenario in which only the trastuzumab originator, not the trastuzumab biosimilar, was listed on the NRML. The alternative scenario assumed that both the trastuzumab originator and biosimilar were placed on the NRML in 2021. Since the biosimilar has similar clinical efficacy and safety to the originator, this budgetary analysis model included only drug costs. The method used to estimate the numbers of breast cancer and gastric cancer patients per year over a 5-year time period in our work was the same as that used in a similar BIA for 28 European countries [32]. However, in this study, we applied epidemiological data and market projected data in China.

Data Sources

The budget impact model was based on epidemiological data, market projected data, and drug cost data per patient treated with the trastuzumab originator and biosimilar in China. The incidence rate and number of new patients with breast cancer and gastric cancer were obtained from the Global Health Data Exchange of the Institute for Health Metrics and Evaluation at the University of Washington, one of the major Global Burden of Disease Research institutions [33]. The numbers of male and female populations were derived from the China National Bureau of Statistics [34]. The market average share of the trastuzumab originator and the proportion of patients currently using the trastuzumab originator were estimated based on the sales data of the trastuzumab originator and the real data of trastuzumab used in hospitals [35–37].

The drug cost data per patient treated with the trastuzumab originator and biosimilar per year over a 5-year time period were calculated based on the unit price of the originator and biosimilar, the corresponding therapeutic regimen of each for each type of cancer, and the average weights of the patients with breast cancer and gastric cancer. The average weights of the patients with breast cancer and gastric cancer were estimated based on the average heights and body mass indexes (BMIs) of Chinese adults, which were obtained from the report on nutrition and chronic disease status of Chinese residents (2020) [38] and the World Health Organization (WHO) [39], respectively.

The model parameters, base-case values and sources or calculation methods used in this study are summarized in Table 1. Detailed explanations of the population data, market projected data and drug cost data of the trastuzumab originator and biosimilar are provided in the following sections.

Table 1
Model parameters, base-case values and sources or calculation methods

Model parameters	Base-case values and sources or calculation methods
Population of China (including females and males)	Population of China during 2000–2019 [33, 34]
Population of China (estimated during 2021–2025)	Assumed a constant rate in annual growth, based on the population of China during 2000–2019 [33, 34]
Epidemiological data including incidence and prevalence in females and males in China (2000–2019)	Epidemiological data from the Global Health Data Exchange [33]
Incidence and prevalence of each of the three cancers in China (2021–2025)	Based on the projected incidence rate (2021–2025) [32], and 5-year prevalence [40]
Proportion of indications among patients	EBC: 88.54%-97%, MBC: 3%-11.46% [41]; MGC: 80.0% [25, 42]
Proportion of HER2-positive patients	EBC: 20%-25%, MBC: 20%-25% [7, 10]; MGC: 12–13% [9, 11–13]
Proportion of patients currently using the trastuzumab originator	30%, Estimated based on available hospital usage data form published literature [35–37]
Trastuzumab originator price	7270 (440mg(20ml)) RMB, Based on the reported price of the Chinese pharmaceutical market in 2019 [43]
Trastuzumab biosimilar price	1688 (150mg) RMB, Obtained from the Shanghai Medical Security Bureau [44]
Market share of the trastuzumab originator for target patients	30%, Based on the opened sales data of the trastuzumab originator in China in 2018 and 2019 [45, 46]
Rate of switching from the originator to the biosimilar in the first year	20%, Assumption
Annual growth in the switching rate in subsequent years	10%, Assumption
Average weights of breast cancer and MGC patients	Projected by the ratio of male to female patients, BMI [39], and average height of Chinese people [38]
Range of the sensitivity analysis	± 20%, in addition to the proportion of MBC patients among breast cancer patients (± 58.5%) [41] and price discount of the originator (-20%-0%)

Population

The method used to estimate the population size with epidemiological data was the same as that used in previous studies [32, 47]. The number of incidence cases was projected based on the incidence rate and the population size for the year. The incidence rate of each year was estimated based on the annual percentage change of the incidence rate, which was calculated by fitting a regression line to the natural logarithm of the initial incidence rate. The population size of each year was estimated based on the former population size and population annual growth rate data. The population annual growth rate was assumed to be constant and was calculated according to the former population (2000–2019).

The prevalence number was projected using the number of new patients for the year and the number of patients previously diagnosed and surviving after a 5-year period and adjusted using 5-year survival rates, the same as the method described in a previous study [32]. According to the available literature, the 5-year survival rates of breast cancer and gastric cancer patients in China were approximately 72.7% [48] and 27.4% [49], respectively, similar to the corresponding patient survival data in Europe. Because of the absence of detailed survival data for Chinese people, survival rates in the model were applied to the corresponding data obtained from the European Cancer Information System of the European Commission [40]. An exponential distribution of the survival rate was assumed to estimate the survival rate in subsequent years.

The potential numbers of trastuzumab-treated HER2-positive patients with each type of cancer analyzed per year were projected based on the proportion of target patients with each type of cancer analyzed and the proportion of HER2-positive target patients. The probable real number of patients treated with trastuzumab in the budget impact model was adjusted by the proportion of patients currently using the trastuzumab originator and the market share of the trastuzumab originator for target patients.

Table 2 lists the number of incidence cases and prevalence cases of breast cancer and gastric cancer and the potential numbers and target patients (HER2-positive patients with EBC, MBC and MGC) who were treated with trastuzumab based on indications during the 5-year time period.

Table 2
The number of incidence cases and prevalence cases of breast cancer and gastric cancer and the potential numbers of HER2-positive patients with EBC, MBC and MGC treated with trastuzumab based on indications during the 5-year time period

Year	The number of incidence cases		The number of prevalence cases		The potential numbers of HER2 + patients with trastuzumab			
	Breast cancer	Gastric cancer	Breast cancer	Gastric cancer	indications			
					EBC	MBC	MGC	Total
1	426456	596035	3636471	1495303	759050	59156	149530	967736
2	452070	611153	3815485	1521150	796416	62068	152115	1010599
3	479211	626638	4007584	1549767	836513	65193	154977	1056683
4	507968	642501	4213405	1580848	879475	68542	158085	1106101
5	538439	658750	4433632	1614142	925443	72124	161414	1158981

Market Projection And Assumptions

Based on the available data of trastuzumab usage in hospitals in the real world [35–37], the model first assumed that 30% of the target population was currently using the trastuzumab originator. Based on the market sales data of trastuzumab in China in 2018 and 2019 [45, 46], the model estimated that the average market volume shares of the trastuzumab originator, not the biosimilar approved in the reference scenario, were approximately 12% in 2018 and 17% in 2019. Thus, the model assumed that the average market share of the trastuzumab originator was 30% and constant over a 5-year time period. In alternative scenario, the study assumed that the rate of switching from the originator to the biosimilar was 20% in the first year, and the annual growth in the rate of switching from the trastuzumab originator to the trastuzumab biosimilar was 10%.

Drug Dosage And Cost

The amounts and costs of consumption per individual were calculated based on the dosage and administration parameters. The model assumed the same dosage and administration parameters for the trastuzumab originator and biosimilar. The doses and administration parameters used in the model and the references are listed in Table 3. The model considered only the direct drug costs. Regarding the price of the trastuzumab originator, because of price confidentiality agreements in the health care price negotiations in 2021 [14], the model applied the prior agreed purchase price published by the National Healthcare Security Administration [43]. Regarding the price of the trastuzumab biosimilar, the price v was derived from the Shanghai Medical Security Bureau [44]. The model assumed that the prices of both the trastuzumab originator and biosimilar were unchanged over a 5-year time period.

Table 3
Doses and administration parameters used in the model and references

Patients	Therapeutic regimen and references
HER2-positive EBC	Initial dose (4 mg/kg) followed by 51 cycles (2 mg/kg) once weekly until 1 year. Initial dose (8 mg/kg) followed by 6 mg/kg for 16 cycles once three weeks until 1 year [18, 41].
HER2-positive MBC	Ignoring previous therapeutic regimens, an initial dose (4 mg/kg) followed by 2 mg/kg for 35 cycles once weekly until approximately eight months. Initial dose of 8 mg/kg followed by 11 cycles (6 mg/kg) once three weeks for until approximately eight months [23, 41, 50].
HER2-positive MGC	Initial dose (8 mg/kg) followed by 6 mg/kg for seven cycles with a 3-weekly therapeutic regimen [24, 25].

Sensitivity Analyses

One-way sensitivity analyses were conducted to assess inherent uncertainty in the data and therefore the robustness of the predicted budgetary savings. Sensitivity analyses were performed with a ± 20% range of input parameters, in addition to the proportion of MBC patients among breast cancer patients, due to its reported range [41] (out of the base-case value ± 20% range) and a -20%-0% price of the originator relative to the unchanged trastuzumab originator, since it usually decreases rather than increases after the introduction of a biosimilar. The sensitivity analysis parameters, base-case values and ranges are listed in table 4.

Table 4

Sensitivity analysis parameters, base-case values and ranges

Sensitivity analysis parameters	Base-case values and ranges
Discounted price of the originator price introduction of the biosimilar relative to the unchanged price of the originator	0 (-20%-0%)
Discounted price of the biosimilar relative to the unchanged price of the originator	31.89% (25.51%-38.27%)
Proportion of patients currently using the trastuzumab originator	30% (24%-36%)
Average market share of the trastuzumab originator	30% (24%-36%)
Rate of switching from the originator to the biosimilar in the first year	20% (16%-24%)
Annual growth in the switching rate in subsequent years	10% (8%-12%)
Proportion of HER2-positive EBC and MBC patients	22.5% (18%-27%)
Proportion of HER2-positive MGC patients	12.5% (10%-15%)
Number of cycles of subsequent doses for MGC	7 (5.6-8.4)
Number of cycles of subsequent doses for MBC	35 (28-42)
Average weight of breast cancer patients	60.29 (48.23-72.35)
Average weight of MGC patients	65.55 (52.44-78.66)
Proportion of MBC patients among breast cancer patients	7.23% (3%-11.46%) [41]

Results

The cost savings results of the budget impact analysis of switching from the trastuzumab originator to the trastuzumab biosimilar from a Chinese payer's perspective, as well as cost savings for additional people treated with the biosimilar are displayed in Table 5.

Based on the presented budget model, in the first year after introduction of the trastuzumab biosimilar, drug cost savings were 0.59 billion RMB and 1.03 billion RMB in the fifth year. The total cost savings was 3.97 billion RMB over 5 years. The number of additional people to treat with biosimilars as drug cost savings would be 9005–15762 over 5 years. Most of the projected cost savings refer to the treatment of HER2-positive EBC (approximately 86%).

Table 5
Budget results (billion RMB) from a Chinese payer's perspective as well as cost savings for additional people treated with the biosimilar

Year	Cost savings from a Chinese payer's perspective				Cost savings for additional people			
	EBC	MBC	MGC	Total	EBC	MBC	MGC	Total
1	0.50	0.03	0.06	0.59	6864	617	1524	9005
2	0.58	0.04	0.06	0.67	7922	712	1705	10339
3	0.66	0.04	0.07	0.78	9153	822	1911	11887
4	0.77	0.05	0.08	0.90	10586	951	2144	13681
5	0.89	0.06	0.09	1.03	12253	1101	2408	15762
Total	3.40	0.21	0.36	3.97	46778	4203	9692	60674

Sensitivity analyses

The one-way sensitivity analysis conducted on model parameters (Fig. 1) showed that the prices of the trastuzumab originator and biosimilar, proportion of patients currently using the trastuzumab originator, market share of the trastuzumab originator, rate of switching from the originator to the biosimilar in first year, average weight of breast cancer patients, and proportion of HER2-positive EBC and MBC patients were the most sensitive factors, whereas the effects of interchanging annual growth in the switching rate in subsequent years, average weight of MGC patients, proportion of HER2-positive MGC patients, number of medication cycles for MGC and MBC, and proportion of MBC patients among breast cancer patients were marginal.

Discussion

This study was a 5-year (2021–2025) budget impact analysis of interchangeability and substitution between the trastuzumab originator and biosimilar from a Chinese payer's perspective. Based on the presented model, the drug cost budget savings could be 0.59 billion RMB in the first year and 1.03 billion RMB in the fifth year, equivalent to approximately 14% and 25% of the total sales of the trastuzumab originator (¥4.29 billion RMB) in China in 2019 [46]. The number of additional people who could be treated with the biosimilar, according to drug cost savings, could be 9005–15762 patients.

Concerning the model parameters, 30% of patients currently using the trastuzumab originator, 30% of the market share of the trastuzumab originator, a 20% rate of switching from the originator to the biosimilar in the first year and a 10% annual growth rate in the rate of switching in subsequent years (approximately 0.20%-0.29% over 5 years), were well conservative figures relative to previous similar budget impact studies [32, 51]. For instance, in the BIA for 28 European countries, it was assumed that 50% of patients are currently using the originator and that the market share of the originator was 42.5%-92.5% [32]; in Croatia, the average rate of switching was 50%, and in other countries, the market uptake of the biosimilar was 30%-80% (approximately 30% in Germany and 90% in Spain) [51]. Based on prior studies on the trastuzumab originator used in 155 hospitals in 29 provinces/cities in China [37], approximately 29.8% of patients currently use the trastuzumab originator in neoadjuvant/adjuvant therapy for HER2-positive breast cancer. However, the treatment rate varies in different cities. Cities and provinces with patients holding medical insurance provide targeted therapy at higher rates (approximately 61.2%), and the proportion of patients with no medical insurance who are treated is 24.9%. It has been reported that the rate of trastuzumab use in developed countries has increased progressively during the past decade [52, 53]. Considering that trastuzumab is presently listed on the NRML, if the rate of treatment with trastuzumab has greatly increased due to the healthcare reimbursement policy in China, the rate of switching to the biosimilar has increased under the Chinese national policy incentive, and if there is an increase in the number of incidence cases of breast cancer and gastric cancer in China, the total drug budget savings would be even more significant.

The comparison of our results to those in the literature remains difficult since, to the best of our knowledge, this is the first published study estimating the budget impact of switching to the trastuzumab biosimilar for the treatment of HER2-positive EBC, MBC, and MGC patients in China. However, similar BIAs have been conducted for the infliximab biosimilar and trastuzumab biosimilar [32, 54–57]. For instance, with regard to the trastuzumab biosimilar, there are four BIAs on switching from an originator to a biosimilar published in peer-reviewed journals: one for Croatia [51], one for 28 European countries [32], one for EU-5 markets [56], and one for the treatment of HER2-positive MBC patients in Shanghai, China (abstract only) [54]. The results of all these BIAs cannot be compared with our results due to the different countries, study years and treatment indication model parameters inputted. However, all these previous studies confirmed that the introduction of a biosimilar could greatly reduce drug costs and benefit more patients [32, 54–57].

The sensitivity analysis on the model parameters in this study was similar to that in previous studies. The price of the trastuzumab biosimilar [57, 58], numbers of target patients and patients currently using the originator [51, 55, 57], rate of switching to the biosimilar and weight of patients [51, 56] are major factors that impact budget savings. The one-way sensitivity analysis confirmed that the percent discount of the biosimilar and originator (relative to the unchanged price of the originator) after introduction of the biosimilar (± 18.19% and − 59.12%, respectively), proportion of patients currently using the trastuzumab originator (± 20%), market share of the trastuzumab originator (± 20%), rate of switching from the originator to the biosimilar in first of year (± 20%), proportion of HER2-positive EBC and MBC patients (± 18.19%), and average weight of breast cancer patients (-20.30%-16.34%) have the greatest impact on budget savings, whereas the effects of interchanging annual growth in the switching rate in subsequent years, average weight of MGC patients, proportion of HER2-positive MGC patients, number of cycles of subsequent doses for MBC and MGC, and proportion of MBC patients among breast cancer patients are only marginal. In addition, the results of the major drug cost savings analysis referring to the treatment of HER2-positive EBC patients (approximately 86%) are similar to those of a previous study [32]. The results of this study are consistent with the medical insurance policy

of controlling expensive drug costs in China, which is to limit medical insurance payments to no more than 12 months for patients with HER2-positive breast cancer after surgery.

Limitations

Several limitations of this budget impact model should be considered. First, this analysis was a partial evaluation of the impact of the trastuzumab biosimilar, since efficacy criteria are not usually included in such analyses. Because it is an international rule to conduct a consistency evaluation between a biosimilar and an originator before approval, this study considered only the difference in drug cost and not efficacy. The current study also did not consider the costs of drug administration and drug loss in the model. Second, this study made some assumptions for model parameters inputted for the calculation. For instance, because the real price of the originator is unavailable (due to the price confidentiality agreement of discounts and rebates (2021)) [14], the model assumed that the merchant's price of the original trastuzumab remained unchanged and applied the previous agreement price (2019) from the National Healthcare Security administration [43]. Finally, 30% of the base-case percent value of patients currently using the trastuzumab originator for HER2-positive breast cancer and gastric cancer remained difficult to estimate concerning the heterogeneous data on the trastuzumab originator in the literature from different and limited hospitals. In addition, the available literature = neglected patient compliance [35–37]. Therefore, all the factors mentioned above may have an unpredictable impact on the results of the budget analysis.

Conclusion

China has a large population, and the incidences of breast cancer and gastric cancer are increasing. The introduction, switching and penetration of the trastuzumab biosimilar in China could greatly promote better access to biological therapy for patients with trastuzumab indications and significant budget savings, therefore improving patient outcomes and benefiting more people. Most of the drug cost savings refer to the treatment of HER2-positive EBC, and further studies can focus on improving the refined management of drug prescriptions, especially for HER2-positive EBC, and therefore improve the efficiency of drug costs. It is also necessary to further investigate and follow up drug usage for the trastuzumab originator and biosimilar trastuzumab in the real world.

Abbreviations

HER2: human epidermal growth factor receptor 2; EBC: early breast cancer; MBC: metastatic breast cancer; MGC: metastatic gastric cancer; NCCN: National Comprehensive Cancer Network; NRML: National Reimbursement Medicine List; BIA: budget impact analysis; NMPA: National Medical Products Administration; ISPOR: International Society for Pharmacoeconomics and Outcomes Research; BMI: body mass index; WHO: World Health Organization

Declarations

Acknowledgments

Not applicable.

Authors' Contributions

YC and GR designed this work. GR and ZY were involved in data collection and developing and running the model. GR calibrated and interpreted the model results and wrote the manuscript. YC and ZH polished the manuscript. All authors have read and approved the manuscript.

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Availability of data and materials

The data used and/or analyzed during this work are available from the corresponding author on reasonable request. You can also available the raw data in the references of this published article, placing your personal data and the information to be requested or its supplemental information files.

Ethics approval and consent to participate

Not applicable.

Consent for publishing

Not applicable.

Competing interests

The authors declare no conflicts of interest.

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Figures

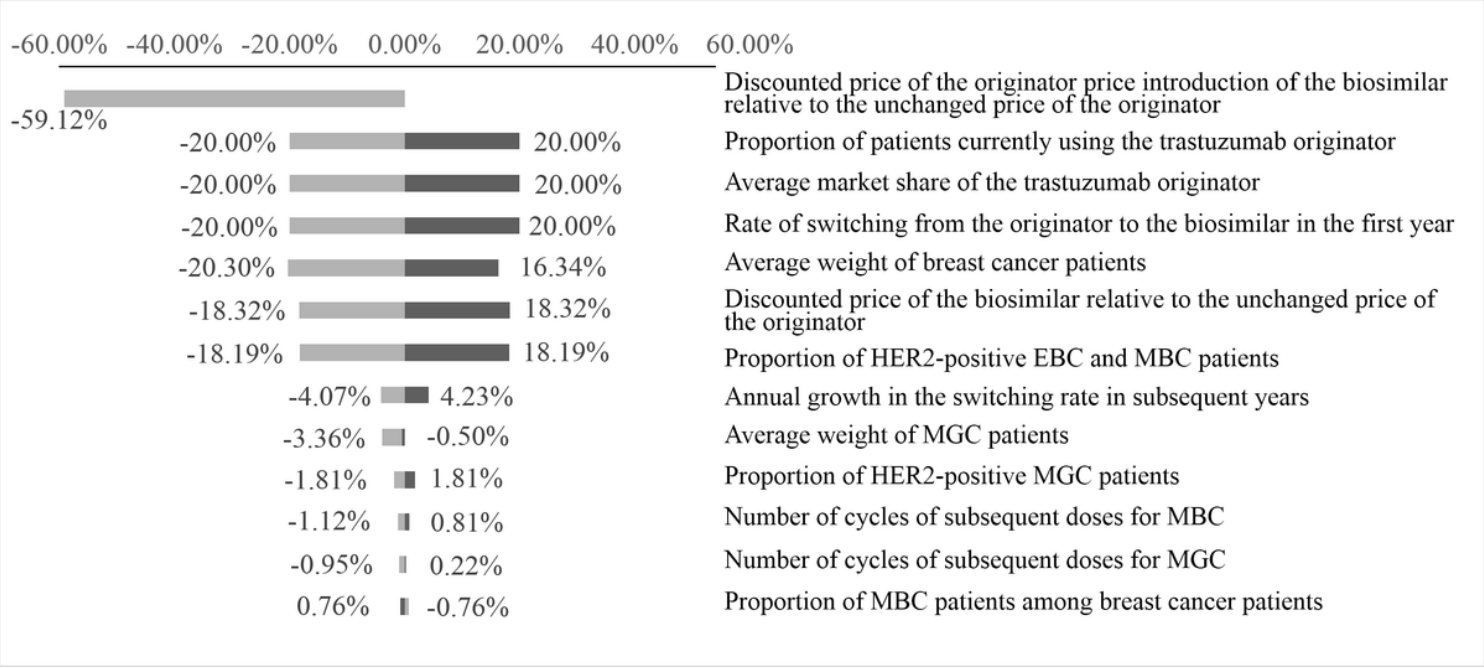

Figure 1

One-way sensitivity analysis conducted on model parameters

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