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ORIGINAL RESEARCH ARTICLE

Budget Impact Analysis of Biosimilar Trastuzumab for the Treatment of Breast Cancer in Croatia

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Abstract

Background and Objective Breast cancer is the most common cancer in women and has considerable impact on healthcare budgets and patients' quality of life. Trastuzumab (Herceptin®) is a monoclonal antibody directed against the human epidermal growth factor receptor (HER2) for the treatment of breast cancer. Several trastuzumab biosimilars are currently in development. In 2015, trastuzumab was the drug with the highest financial consumption among all drugs in Croatia. This model estimates the 1-year budget impact of the introduction of biosimilar trastuzumab in Croatia.

Methods A budget impact model, based on approvals for trastuzumab treatment in 2015, was developed for the introduction of biosimilars. Two biosimilar scenarios were developed: biosimilar scenario 1, based on all approvals in 2015, and biosimilar scenario 2, based on approvals after February 2015 and the reimbursement of the subcutaneous formulation of trastuzumab in Croatia. Only trastuzumab-naïve patients and drug-acquisition costs were used in the model. Uptake of biosimilar was assumed at 50 %. Scenarios were calculated with price discounts of 15, 25 and 35 %. The robustness of the model was tested by extensive sensitivity analyses.

Results The projected drug cost savings from the introduction of biosimilar trastuzumab range from €0.26 million (scenario 2, 15 % price discount) to €0.69 million (scenario 1, 35 % price discount). If budget savings were reinvested to treat additional patients with trastuzumab, 14 (scenario 2, 15 % price discount) to 47 (scenario 1, 35 % price discount) additional patients could be treated. Sensitivity analyses showed that the incidence of breast cancer had the highest impact on the model, with a 10 % decrease in incidence leading to an 11.3 % decrease in projected savings.

Conclusion The introduction of biosimilar trastuzumab could lead to significant drug cost savings in Croatia.

Key Points for Decision Makers

In 2015, trastuzumab (Herceptin®; Roche) was the drug with the highest financial consumption among all drugs in Croatia, with sales of approximately €10.6 million.

Several trastuzumab biosimilars are currently in development.

Depending on the scenario, projected drug cost savings from the introduction of biosimilar trastuzumab in Croatia could range from €0.26 million to €0.69 million in the first year, which would allow for the treatment of 14–47 additional patients.

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1 Introduction

Breast cancer is the most common cancer among women, both in more and less developed regions [1]. In 2012, there were approximately 464,000 new cases and 131,000 deaths from breast cancer in Europe [2]. In the Republic of Croatia, breast cancer was the fourth highest cause of death among women and ninth highest in both sexes in 2014 [3].

The disease has considerable economic impact on healthcare budgets and patients' quality of life, with the second highest economic cost (€15 billion, 12 % of overall cancer costs) and third highest productivity losses attributable to mortality (€3.25 billion) annually among all cancers across the EU [4]. Women of working age are especially affected by the disease, facing greater risk for psychosocial adjustment problems and higher productivity losses from disability, number of missed working days and days stayed in bed than individuals without a cancer history [5–7].

Approximately 20–25 % of breast cancer cases have overexpression, amplification or both of the human epidermal growth factor receptor (HER2), a member of the epidermal growth factor receptor family [8, 9]. HER2-positive tumours are associated with a shorter time to disease relapse and lower overall survival, with the possible reduction of the average period of survival after diagnosis of metastatic breast cancer up to 50 % [9–11].

Trastuzumab (Herceptin®; Roche) received marketing authorization for the EU in 2000 [12]. It is a monoclonal antibody (mAb) directed against the HER2, indicated for the treatment of early breast cancer, metastatic breast cancer and metastatic gastric cancer [13, 14]. Trastuzumab can only be prescribed when the cancer has been shown to overexpress HER2. The clinical effectiveness and safety of trastuzumab in the treatment of early and metastatic breast cancer is supported by numerous clinical studies [15–17]. In 2013, trastuzumab received marketing authorisation for subcutaneous injection, an alternative formulation to trastuzumab intravenous transfusion [18].

In recent years, the number of approved mAb products and their sales have increased significantly [19]. Due to the growing number of available mAb drugs and high cost of treatment, these drugs have a great impact on healthcare expenditures, and access to patients may become limited [20, 21]. The introduction of biosimilars could lower costs of treatment and increase access to therapy [22].

A biosimilar is a biological medicinal product that contains an active substance highly similar to an already authorised original (reference) biological medicinal product [23, 24]. Because of the complexity of biological molecules and their production, it is hardly possible to make an exact copy of the reference product. Therefore, biosimilarity of the product has to be established in terms of quality, biological activity, safety and efficacy [23].

In the case of mAbs, such as trastuzumab, biosimilars should be similar to the reference mAb in physicochemical and biological terms, with justification of observed relevant differences [23, 25]. The European Medicines Agency (EMA) approved the first two mAb biosimilars in 2013 (biosimilars of infliximab) [26]. Regarding Herceptin, patents in Europe expired in 2014 and trastuzumab biosimilars are already in development, with two products already on the market in South Korea and Russia [27–29].

Biosimilar trastuzumab (Herzuma™; Celltrion, Inc.) is a biosimilar of Herceptin that is the most advanced molecule in development, marketed in South Korea following approval from the national Ministry of Food and Drug Safety in 2014 [28, 30]. Herzuma is supported by one phase III study in patients with metastatic breast cancer (COMPARE; ClinicalTrials.gov #NCT01084876). The study showed equivalent efficacy of Herzuma to trastuzumab in terms of overall response in combination with paclitaxel and a safety profile comparable to that of trastuzumab [31]. Another biosimilar trastuzumab (HERticad™; Biocad) is marketed in Russia, after receiving approval from the Ministry of Health of the Russian Federation [32].

Although no trastuzumab biosimilar is currently approved by the EMA, the potential savings associated with biosimilar introduction could be significant. In 2015, trastuzumab was the drug with the highest financial consumption among all drugs in Croatia, with sales of approximately €10.6 million [33]. Therefore, the potential financial savings in the Croatian healthcare system could be significant. In this paper, we designed a budget impact model to estimate the financial impact of the introduction of trastuzumab biosimilar in the Republic of Croatia.

2 Methods

This budget impact analysis estimated the financial impact of the introduction of biosimilar trastuzumab for the treatment of early and metastatic breast cancer in Croatia over a 1-year time horizon. The model adopts the perspective of the public healthcare budget in Croatia and considers biosimilar introduction only for the intravenous formulation of trastuzumab.

2.1 Setting

In the Republic of Croatia, mandatory health insurance is provided by the Croatian Health Insurance Fund (CHIF). The CHIF is responsible for the reimbursement of

medicines, with medicines placed on one of two lists: a basic list (essential medicines, provided free of charge to the patients) and a complementary list (medicines are partially covered by CHIF and partially by out-of-pocket payments by patients). Medicines on the basic list are reimbursed by mandatory health insurance, either by the CHIF's budget (primary healthcare and outpatient care) or the hospital's budget (inpatient hospital care).

Additionally, certain medicines from this list are also included in the list of high-priced medicines and are reimbursed by a separate budget item of the CHIF [34, 35]. In order to limit expenditure, most of high-priced medicines have special Managed Entry Agreements (MEAs) with the CHIF. There is no price limit to enter the list, but the product must be intended for hospital use, it has to show a breakthrough in the risk–benefit ratio of treatment for a given indication, and a budget impact analysis has to show that the product could not be financed by the routine hospital budget [35]. In order to be reimbursed by the CHIF, treatment with a high-priced medicine has to be approved by the hospital committee for medicines and medicinal products and then reviewed by the CHIF. In 2015, the budget of the CHIF for high-priced medicines was €105 million.

One of the medicines reimbursed from this list in Croatia is trastuzumab; the intravenous formulation from 2006 and the subcutaneous formulation from 28 February 2015. Every trastuzumab treatment for breast cancer has to be reviewed and approved by the CHIF. All approved treatments are stored in the CHIF's databases.

In the case of early breast cancer, treatment is approved for 17 cycles. For metastatic breast cancer, treatment is approved for six cycles and continued until disease progression, with regular specialist checkups and treatment extensions every six cycles. Based on hospital and chemotherapy protocols, some patients can switch from intravenous to subcutaneous trastuzumab (or vice versa).

The indication of metastatic gastric cancer is not reimbursed by the CHIF and can be funded only from the hospital budget. The treatment is approved by the hospital committee for medicines and medicinal products, but is not reviewed by the CHIF, and approval is not stored in the CHIF's databases.

2.2 Data Analysis and Modelling

This model is built on the approvals for trastuzumab breast cancer treatment in Croatia for 2015, which were extracted from the CHIF's databases. Retrieved data were anonymous and analysed using Excel. The treatment approvals, prerequisite for the start of the treatment, have been chosen in order to correctly determine the indication of the patients.

Since treatment indication is not recorded during the approval process, each approval was checked individually, and the approved number of cycles (17 cycles for early breast cancer and 6 cycles or multiple approvals of 6 cycles for the treatment of metastatic breast cancer) was the key information for determining indication. Data were retrieved for 2015, the last available calendar year, and it was assumed that all patients who gained approval had started their treatment.

Due to the uncertainty around the interchangeability of originator mAbs with biosimilars and therefore future uncertainty regarding the interchangeability of originator trastuzumab with biosimilars, our budget impact model considers only trastuzumab-naïve patients. The model flow diagram is presented in Fig. 1. After excluding all patients who gained approval for treatment in 2015 but were treated with trastuzumab in 2014, 479 patients were identified as trastuzumab-naïve patients in 2015. All patients were included in the model, but since the model assumes biosimilar introduction only for the intravenous formulation of trastuzumab, the price of the subcutaneous formulation was fixed in all scenarios. Therefore, the net financial impact of patients with the subcutaneous formulation was zero in the whole model.

Since the subcutaneous formulation of trastuzumab has been reimbursed in Croatia from the beginning of March 2015 and has influenced treatment options, two scenarios were considered:

- Biosimilar scenario 1: all trastuzumab-naïve patients in 2015 were considered in the model.
- Biosimilar scenario 2: only trastuzumab-naïve patients with treatment approval after February 2015, when subcutaneous trastuzumab started being reimbursed by the CHIF, were considered.

The number of patients and their treatment options were then projected over the whole year. This scenario reflects the fact that patients who started treatment in January and February could only be treated with the intravenous formulation of trastuzumab, which might overestimate the number of patients who could switch to a biosimilar.

2.3 Population

Population of interest (Table 1) comprised trastuzumab-naïve patients. The numbers of patients with early and metastatic breast cancers treated with trastuzumab are based on treatment approval data of the CHIF for 2015. It was assumed that all patients start their treatment at the beginning of the year and that the total number of patients in the model is the same with and without the trastuzumab biosimilar.

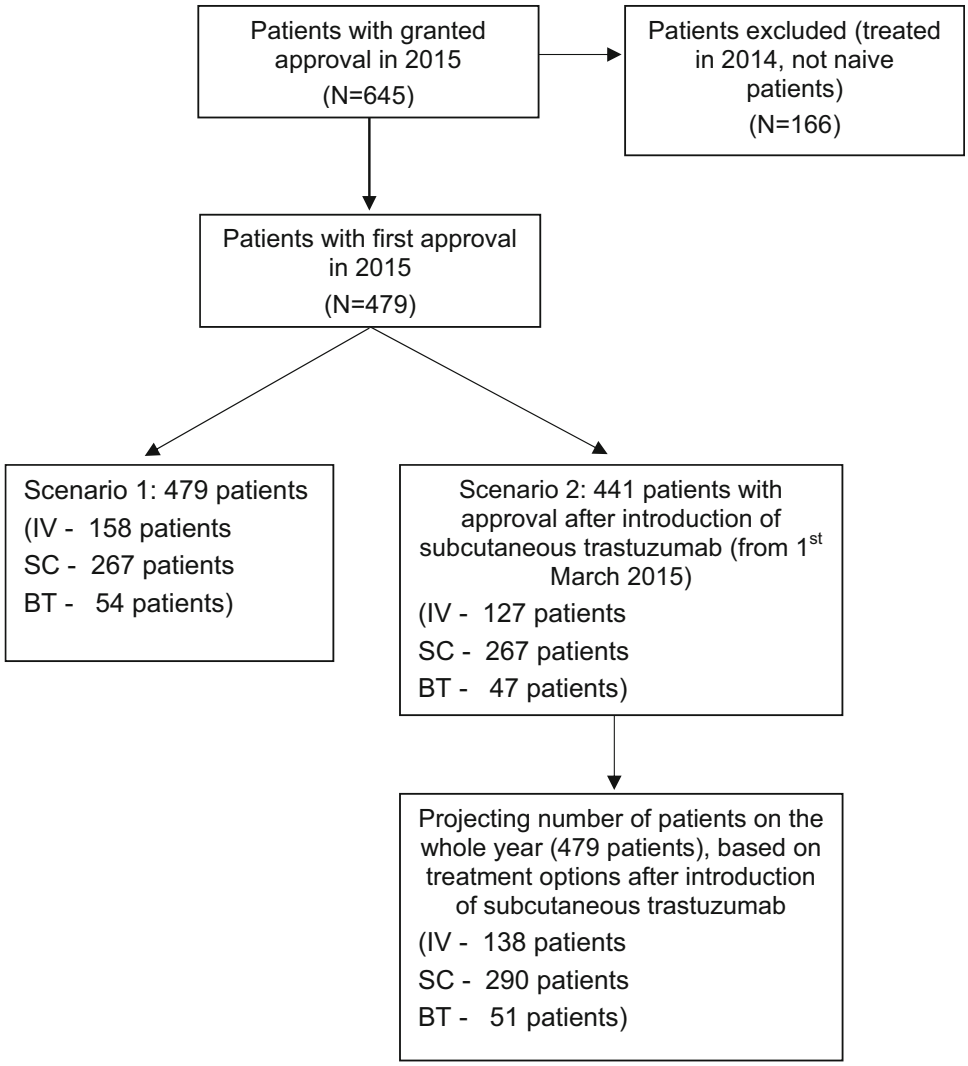

Fig. 1 Model flow diagram: calculation of the number of trastuzumab-naïve patients in Croatia. *N* number of patients, *IV* intravenous trastuzumab formulation, *SC* subcutaneous trastuzumab formulation, *BT* both trastuzumab formulations

Table 1 Model inputs: number of patients and average number of doses for both trastuzumab formulations

Variables	Early BC	Metastatic BC
Number of patients: scenario 1 (scenario 2)		
Intravenous trastuzumab formulation	125 (108)	33 (30)
Subcutaneous trastuzumab formulation	216 (235)	51 (55)
Both trastuzumab formulations	44 (41)	10 (10)
Number of cycles (both scenarios)		
Intravenous trastuzumab formulation	15	8
Subcutaneous trastuzumab formulation	15	8
Both trastuzumab formulations		
Intravenous trastuzumab formulation	4	3
Subcutaneous trastuzumab formulation	11	9

Granted approvals for trastuzumab treatment in 2015 in Croatia (Croatian Health Insurance Fund's database)

BC breast cancer

The annual number of 2584 new breast cancer cases in Croatia, used in the sensitivity analyses, was derived from the latest published Croatian National Cancer Registry of the Croatian Institute of Public Health [36]. Sensitivity analyses, in which the number of newly diagnosed breast cancer patients varied by ±10 %, assumed that the

percentage of newly diagnosed breast cancer patients treated with trastuzumab remains the same as in the two considered scenarios (479 trastuzumab-naïve patients/2584 new breast cancer cases, i.e. 18.53 %).

The number of treatment cycles was derived from the approved trastuzumab treatments in the CHIF's databases. According to clinical trials and treatment in routine practice, treatment of early breast cancer is discontinued before 1 year in between 2.6 and 15 % of patients, mostly because of cardiac dysfunction [13, 15, 37]. Therefore, the number of cycles for the adjuvant setting in the model was decreased by 10 % (i.e. from 17 to 15 cycles). It was assumed that patients with metastatic breast cancer use all approved doses.

Doses and administration schedules for trastuzumab originator and biosimilar were taken from the Herceptin Summary of Product Characteristics (SPC). Uptake of biosimilar was assumed at 50 %. The model assumed 3-weekly scheduling of medicines, with the initial loading dose of 8 mg/kg of body weight and a maintenance dose of 6 mg/kg [14]. Due to the lack of data about breast cancer patient weight in Croatia, the average weight of patients was estimated at 70 kg, based on data from clinical trials [38, 39]. The same body weight was also assumed in health technology assessments conducted in the UK by the National Institute for Health and Care Excellence (NICE) and Scottish Medicines Consortium (SMC) [40, 41].

2.4 Costs

The price of the intravenous formulation of trastuzumab, €588.29 including value-added tax, was taken from the published list of basic medicines of the CHIF [42]. Medicine prices in Croatia are set up by special ordinance, and the maximum price of the first biosimilar cannot exceed 85 % of the originator price, i.e. the price of the biosimilar has to be at least 15 % lower [43–45]. Therefore, this model analyses the financial impact of a biosimilar with a 15 % price discount as the lowest price discount, and further analyses were conducted for the price discounts of 25 and 35 %.

Our model considered only drug acquisition costs. All other costs (e.g. adverse events, costs of administration) were assumed to be the same for trastuzumab originator and biosimilar. Dosing and administration were assumed to be the same for both drugs. It was assumed that all patients treated with intravenous trastuzumab, both as monotherapy and in combination with subcutaneous trastuzumab, receive a loading dose. The model is based on cost-efficient use of vials, i.e. the unused dose of one patient is administered to the next patient.

All costs and financial savings were estimated in Croatian kuna (HRK) and then converted to Euros (€1.00 = HRK7.609601), based on the annual midpoint exchange rate of the Croatian National Bank for 2015 [46].

2.5 Sensitivity Analyses

The robustness of the model was tested by one-way sensitivity analyses. Parameters varied in the sensitivity analyses included uptake of biosimilar (±10 %), incidence (±10 %), number of patients on intravenous trastuzumab (±10 %), patient weight (±10 %) and number of cycles (±1).

3 Results

Model findings, presented in Table 2, show that introduction of an intravenous trastuzumab biosimilar would lead to drug cost savings in the first year after introduction, ranging from €0.26 million for biosimilar scenario 2 (15 % price discount) to €0.69 million for biosimilar scenario 1 (35 % price discount). Most of the projected savings refer to the indication of early breast cancer. Due to the higher number of patients on intravenous trastuzumab, savings were higher for biosimilar scenario 1 in all analyses.

Projected drug costs savings could be used to treat additional patients with biosimilar. Depending on the scenario, the number of additional patients might range from 14 (15 % price discount) to 47 (35 % price discount). Therefore, in the case of future growth of annual number of approvals for treatment, 3–10 % of additional patients could be treated with trastuzumab biosimilar if projected drug cost savings were reinvested in treatment with trastuzumab.

3.1 Sensitivity Analyses

The results of the sensitivity analyses for biosimilar scenario 2 are shown in Fig. 2 (15 % price discount), Fig. 3 (25 % price discount) and Fig. 4 (35 % price discount). The highest total impact on projected savings was calculated by changing the incidence of breast cancer. A 10 % decrease of incidence would lead to an 11.3 % decrease in projected savings, and a 10 % increase of incidence would lead to a 9.7 % increase in projected savings. Changing number of cycles by one had the smallest impact on the savings.

Results of the calculated sensitivity analyses show high robustness of the model results, and variation of all model parameters had a similar financial impact on projected savings. This can be contributed to the design of the model,

Table 2 Results of the model and scenario analyses

	Drug cost savings (€)			Additional BC patients on trastuzumab if budget savings were spent on biosimilar		
	Early BC	Metastatic BC	Total	Early BC	Metastatic BC	Total
15 % discount scenario						
Biosimilar scenario 1	258,466	36,474	294,940	12	3	15
Biosimilar scenario 2	225,992	34,444	260,436	11	3	14
25 % discount scenario						
Biosimilar scenario 1	430,776	61,182	491,958	23	6	29
Biosimilar scenario 2	376,653	57,800	434,453	20	6	26
35 % discount scenario						
Biosimilar scenario 1	603,087	85,890	688,977	37	10	47
Biosimilar scenario 2	527,315	81,155	608,470	32	9	41

BC breast cancer

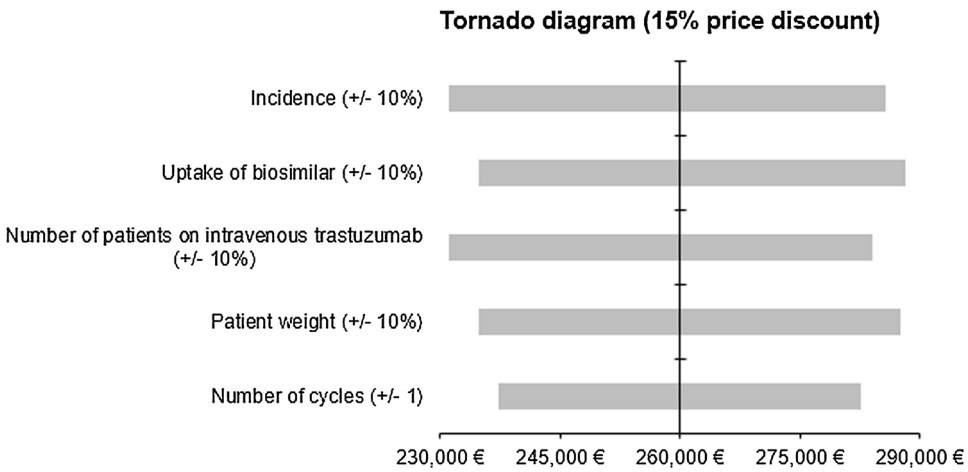

Fig. 2 One-way sensitivity results (financial savings) of biosimilar scenario 2 (15 % price discount)

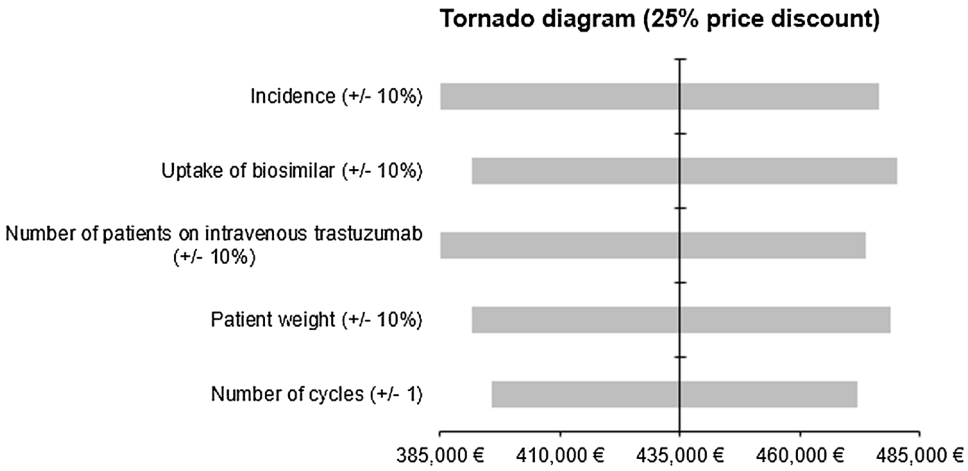

Fig. 3 One-way sensitivity results (financial savings) of biosimilar scenario 2 (25 % price discount)

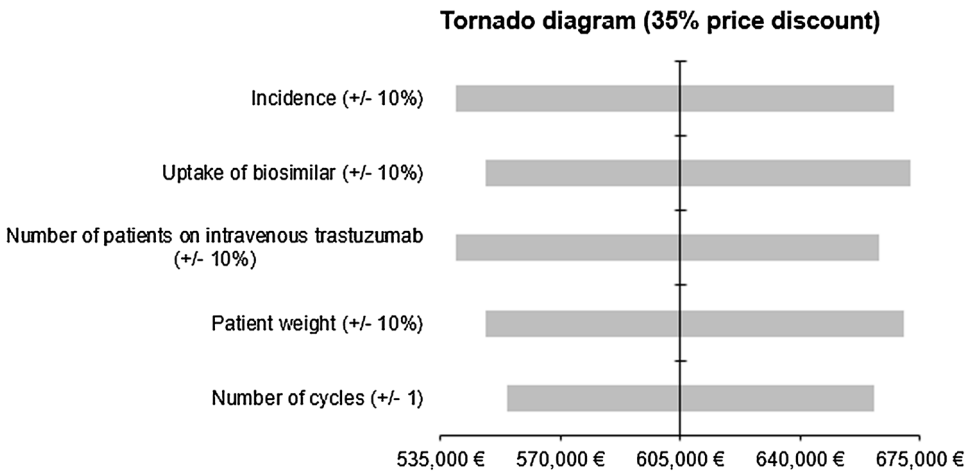

Fig. 4 One-way sensitivity results (financial savings) of biosimilar scenario 2 (35 % price discount)

which does not allow interchangeability of medicines and considers only trastuzumab-naïve patients.

4 Discussion

This study estimated the budget impact of biosimilar trastuzumab on the healthcare budget in Croatia. Our results suggest that introduction of biosimilars could lead to considerable drug cost savings, varying from €0.26 million with a 15 % price discount to €0.69 million with a 35 % price discount. This finding is supported by several sensitivity analyses, which confirmed high robustness of the model. If potential drug costs savings were used to treat additional patients with biosimilar, an additional 11 early and 3 metastatic breast cancer patients could be treated in biosimilar scenario 2 with 15 % price discount.

The sales of trastuzumab in Croatia are approximately €10.6 million annually [33]. According to the calculations in this budget impact analysis, introduction of a biosimilar could decrease total financial consumption of trastuzumab by 2.4–6.3 % in the first year, depending on the biosimilar discount. While first-year savings could be important in reducing the pressure of healthcare expenditure on the public budget in Croatia, potential savings in second and further years could actually be much higher. Based on the ordinances that regulate price of medicines in Croatia, medicine prices are annually, at least once, subjected to the internal reference pricing system adjustment [43–45].

The system compares prices of medicines on the basis of the Anatomical Therapeutic Chemical (ATC) classification (ATC level III–V), and prices of the same medicines by the ATC classification following referencing have to be reduced to the lowest priced molecule in the class [47]. Therefore, the price of intravenous Herceptin would have to be reduced to the price of the biosimilar, leading to potential savings of €0.52 million (4.8 % of total trastuzumab consumption; 15 % price discount) to €1.39 million (12.7 % of total trastuzumab consumption; 35 % price discount). If the price of subcutaneous trastuzumab would also be lowered, the financial saving would be even more significant.

Similar budget impact analyses have been conducted for the biosimilar infliximab, which has already been approved by the EMA. Two studies, both conducted for selected European countries, have concluded that introduction of infliximab biosimilar could lead to considerable drug costs saving and wider patient access [48, 49]. The annual cost savings resulting from the introduction of a biosimilar were projected to range from €2.89 million (Belgium, 10 % discount) to €33.80 million (Germany, 30 % discount), and the size of the initial population (number of patients treated in the model) had the biggest impact on the financial savings [49].

Our analysis is limited by the fact that none of the trastuzumab biosimilars have so far been approved by the EMA in the EU. Due to the complexity of mAbs, there are several issues in the process of regulatory agencies approving biosimilars that are relevant for their clinical usage. Firstly, the most sensitive patient population is preferred in clinical trials to detect potential differences between originator and biosimilar [23]. In the case of trastuzumab biosimilars, due to the confounding factors of metastatic setting, early breast cancer could be more sensitive and homogenous for conducting clinical trials [28, 50].

Secondly, selection of clinical endpoints is also a challenge in the case of trastuzumab biosimilars. According to the EMA, the most sensitive clinical endpoint is preferred in order to be able to detect product-related differences [23]. Since numerous factors beyond medicine could influence survival, clinical endpoints that measure activity, such as overall response rate (ORR), should be considered as the primary endpoint in most cases over endpoints that

measure survival. The problem is that ORR is not always correlated enough with patient outcomes and survival, endpoints that are very important for the antineoplastic agents [28].

Interchangeability and substitution between originator and biosimilar are also issues that raise concern. Since biosimilars are not identical to, but are indistinguishable from, their originator, interchangeability is questionable. The EMA approves biosimilars and evaluates biosimilar medicines for authorisation purposes, but does not have the authority to label them as interchangeable, leaving the decision to the national medical authorities of each country in the EU [51, 52].

Another limitation of this study is the uncertain market share of intravenous trastuzumab in the future. In 2013, Roche received approval for the subcutaneous version of trastuzumab, which has a pharmacokinetic profile and efficacy that are non-inferior to standard intravenous trastuzumab, with a similar safety profile [39, 53, 54]. Due to the quicker administration and its possible usage outside hospital setting, subcutaneous administration of trastuzumab could reduce medical costs and be preferred by patients. This formulation of trastuzumab is more likely to be used if trastuzumab is not combined with other drugs given intravenously.

Last but not least, our assumptions were made according to the CHIF's adopted policy regarding discounted reimbursement of new biosimilar molecules, while projections regarding dosage regimens and patient weights were made taking into account the relevant health technology assessments and guidelines, as well as SPCs [14, 40, 41]. Regarding biosimilar uptake, in 2013, France became the first European country to pass a law for biosimilar substitution, while the Norwegian government in 2014 set up a clinical study to assess the interchangeability of Remicade (infliximab) and its biosimilar, in which patients are switched from originator to biosimilar forth and back. [55, 56]. In Norway, the tender price of infliximab biosimilar was 70 % lower than originator in 2015, with the market share of biosimilar over 75 % [57, 58].

The choice of treatment with a reference biologic or with a biosimilar remains a clinical decision entrusted to the prescribing physician in most countries. However, in Croatia, hospital committees for medicines and medicinal products have to approve all new treatments with high-priced drugs through evaluation of prescribed expensive treatments with regard to the CHIF's therapeutic guidelines and reimbursement policy as well as assessment of therapeutic cost effectiveness, thus potentially maximizing biosimilar uptake (infliximab, filgrastim, etc.) [42–45]. In cases where originator and biosimilar molecules have the same efficacy and safety profiles, considering potential cost differences other than drug acquisition costs in pharmacoeconomic modelling may not be necessary [31, 59].

Trastuzumab worldwide sales reached almost US$7 billion in 2014, and the market segment of the HER2-positive subtype of breast cancer is expected to grow in the future [60, 61]. Due to the high cost of treatment, access to trastuzumab could be limited for certain patients [62]. Our model shows that introduction of a biosimilar could lower medical costs and increase the number of treated patients in Croatia.

5 Conclusion

According to the presented budget impact model, the introduction of biosimilar trastuzumab could lead to significant drug cost savings in Croatia. The robustness of the model was confirmed by several sensitivity analyses, and variation of all parameters had a similar financial impact on projected savings.

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Compliance with Ethical Standards

This study received no funding.

Conflict of interest Authors August Cesarec and Robert Likić declare that they have no conflict of interest.

Author contributions August Cesarec analysed input data, developed and ran the model and interpreted the results. Robert Likić assisted in the conception and the development of the model. Both authors were involved in drafting and revision of the manuscript.

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