Cost-efficiency and expanded access modeling of conversion to biosimilar trastuzumab-dkst with or without pertuzumab in metastatic breast cancer

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\textbf{ABSTRACT}

\textbf{Aims:} To investigate the cost-efficiency and budget-neutral expanded access of biosimilar intravenous trastuzumab-dkst versus reference intravenous (trastuzumab-IV) and subcutaneous trastuzumab (trastuzumab-SC) (with/without pertuzumab) in metastatic breast cancer (MBC).

\textbf{Methods:} Economic simulation modeling in a panel of 1,000 MBC patients to estimate: 1) cost-savings by conversion from trastuzumab-IV or trastuzumab-SC to trastuzumab-dkst at 10-100\% conversion rates in 3 weight groups: first quartile (Q1:62.2 kg), median (73.1 kg), third quartile (Q3:88.6 kg), and 2) budget-neutral expanded access to trastuzumab-dkst from cost-savings.

\textbf{Results:} In monotherapy, conversion (\%) from trastuzumab-IV generates one-year cost-savings from $2,272,189 (Q1;10\%) to $31,506,804 (Q3;100\%) and from trastuzumab-SC monotherapy savings range from $2,071,277 (Q3;10\%) to $35,775,475 (Q3;100\%). In combination with pertuzumab, trastuzumab-dkst is cost-efficient in all patient weights with one-year savings over trastuzumab-IV up to $32,662,714 (Q3;100\%) and over trastuzumab-SC up to $35,322,461 (Q3;100\%). Savings from conversion from trastuzumab-IV monotherapy could provide between 3,087 (Q1;10\%) and 30,911 (Q3;100\%) additional trastuzumab-dkst doses—enough to treat 58 to 583 patients for one year. Conversion from trastuzumab-SC monotherapy could provide between 1,559 (Q3;10\%) and 48,598 (Q3;100\%) additional trastuzumab-dkst doses or 38 to 918 additional one-year treatments with trastuzumab-dkst. In combination with pertuzumab, conversion from trastuzumab-IV could provide from 311 (Q1;10\%) to 3,939 (Q3;100\%) maintenance doses (pertuzumab + trastuzumab-dkst) or 17 to 210 additional one-year regimens (all agents). Savings from conversion from trastuzumab-SC could expand access to 226 (Q3;10\%) to 4,782 (Q3;100\%) additional maintenance doses or 12 to 254 one-year regimens.

\textbf{Conclusions:} This first cost-efficiency and expanded access study of biosimilar therapeutic cancer agents shows that trastuzumab-dkst is cost-efficient over trastuzumab-IV and trastuzumab-SC across all patient weights in both monotherapy and combination with pertuzumab and paclitaxel. These cost savings could provide more patients with trastuzumab-dkst treatment on a budget-neutral basis.

\textbf{Introduction}

Therapeutic biologics in oncology, such as targeted monoclonal antibodies, immune checkpoint inhibitors, and cell therapies have significantly advanced cancer treatment options and outcomes, however, at a significant incremental cost. With the expiration of the patents of the first generation of therapeutic monoclonal antibodies in oncology, the development of biosimilar therapeutics is accelerating\textsuperscript{1}. There is a concomitant need to investigate the potential cost-efficiency offered by therapeutic biosimilars and to assess their potential impact on healthcare and market dynamics. Our previous pharmacoeconomic studies have demonstrated the potential cost-efficiency, the opportunities for budget-neutral (that is, from the accrued savings, without further impact on, and within the constraints of, budget) expanded patient access to cancer care, and, more generally, the economic value of biosimilars in the setting of supportive cancer care across various tumor types\textsuperscript{2–9}. Herein, we expand this pharmaco-economic paradigm and report on the first cost-efficiency (and budget-neutral) expanded access simulation analysis in the setting of therapeutic monoclonal antibodies, focusing specifically on conversion from reference trastuzumab (Herceptini\textsuperscript{\textregistered}) to biosimilar trastuzumab-dkst (Ogivri\textsuperscript{\textregistered}).

Trastuzumab targets the human epidermal growth factor receptor 2 (HER2) and is currently approved for the treatment of HER2-positive (HER2\textsuperscript{\textregistered}) early and advanced metastatic breast cancer (MBC)\textsuperscript{\textsuperscript{10}}. The combination of trastuzumab with pertuzumab and taxane-based...
chemotherapy is among the first-line treatment options for metastatic HER2+ breast cancer, especially in the US, and results in overall survival of 56.5 months in chemotherapy-naïve patients compared with 40.8 months in the placebo group. Additionally, trastuzumab monotherapy is approved for treating patients with MBC who have received one or more chemotherapy regimens. It is also used in the adjuvant setting without chemotherapy in selected older patient populations, as well as in the neoadjuvant or adjuvant settings for patients with early HER2+ breast cancer. Recent real-world studies suggest significant disparities in access to anti-HER2 therapy in resource-limited countries due, in part, to the high cost of trastuzumab.

Trastuzumab-dkst (Ogivri) is the first trastuzumab biosimilar approved by the US FDA in December 2017, based in part on the phase 3 HERITAGE trial. In this multicenter, randomized, double-blind, parallel-group equivalence trial, a total of 500 patients were randomized 1:1 to receive trastuzumab-dkst or trastuzumab plus a taxane. Trastuzumab-dkst treatment resulted in an overall response rate (ORR) of 69.6% (95% CI, 63.62%–75.51%) compared with 64.0% (95% CI, 57.81%–70.26%) for reference trastuzumab. The ORR ratio and differences were within the equivalence boundaries. Additionally, at week 48, there was no significant difference between biosimilar trastuzumab-dkst and reference trastuzumab in time to tumor progression, progression-free survival, or overall survival. Trastuzumab-dkst and trastuzumab showed similar adverse event profiles.

The cost-efficiency analysis is a pharmacoeconomic assessment methodology that extends conventional cost-minimization analysis. In the latter, two alternative therapies with effectiveness and safety outcomes known or assumed to be identical are compared exclusively on their direct costs to identify the lowest cost therapy. As we have noted earlier, cost-efficiency analysis takes the cost-minimization analysis a step further in terms of “evaluating the cost of various scenarios of delivering healthcare interventions.” Specifically, “the goal is not to determine the lowest cost, but to find the most efficient cost structure contributing to the value equation” to determine “where and how we can be more (cost-) efficient in our choice of treatment options so that we can achieve better outcomes for less money.” The cost-efficiency analysis is also different from the “classical” types of pharmacoeconomics, such as cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA). These methods assess the incremental cost per unit of outcome achieved but express outcome in different forms: in natural units such as a life-year gained or a death averted (CEA); in generic units such as a quality-adjusted (QALY) or disability-adjusted life gained (DALY) (CUA), or in monetary units (CBA). The cost-efficiency analysis also differs from budget impact analysis (BIA). A BIA assesses changes in expenditures associated with the decision of paying for a new treatment and thus adding a treatment to the covered treatment mix. It typically compares a scenario (“world”) without the new treatment to a scenario (“world”) with the new treatment. This new treatment may be similar or different in efficacy/effectiveness or safety.

In this cost-efficiency analysis of conversion to biosimilar trastuzumab-dkst, it is important to consider the broader frame of savings potentially enabled by biosimilars. A recent European cost-analysis demonstrated that biosimilar trastuzumab products could offer annual savings ranging from €95.9 million to €120.5 million if all patients received the least expensive trastuzumab biosimilar compared to the original drug, however, it did not address the public health benefit of these savings. Hence, and continuing a line of simulation analyses of the cost-efficiency of biosimilar conversion and the expanded access such conversion provides to cancer care on a budget-neutral basis in the setting of supportive cancer care, we now report here on the first such analysis in therapeutic cancer care. Specifically, we examined the cost-efficiency and expanded access of conversion to biosimilar trastuzumab-dkst regimens from reference intravenous (IV) trastuzumab as well as the subcutaneous (SC) formulation of trastuzumab and hyaluronidase-oysk (trastuzumab-SC; Herceptin Hylecta) in a hypothetical panel of 1,000 patients with MBC. We modeled both trastuzumab monotherapy and the combination therapy with pertuzumab (Perjeta) across three patient weight categories over one and two years.

Methods

The goals of this economic simulation were:

- To determine the cost-efficiency of conversion from reference trastuzumab IV or SC to IV biosimilar trastuzumab-dkst with or without pertuzumab.
- To simulate the expanded access to additional treatment with trastuzumab-dkst, with and without pertuzumab, on a budget-neutral basis for both scenarios.

Model

For this economic analysis, a simulation model was developed from the US payer perspective for a panel of 1,000 patients with MBC. We simulated two scenarios, including treatment with or without pertuzumab over one and two years. Each scenario considered several variables, including conversion from reference IV and SC trastuzumab formulations to trastuzumab-dkst at conversion rates of 10%–100% in three patient weight categories. Inputs included per-label administration times for all agents, drug costs, and cost of drug administration.

Assumptions

- This is a time-and-cost-efficiency analysis of reference trastuzumab-IV and trastuzumab-SC vs biosimilar IV (not a cost-effectiveness analysis or cost-utility analysis).
- Analysis was based on the US market and 2020 direct costs in US dollars.
- All trastuzumab treatment options were considered to have equal efficacy and safety. 21–23, 28.
- The chair time, while quantified for infusion time and administration cost does not otherwise have an associated cost (i.e., is not a separately billable item) but may entail an opportunity cost (not quantified).
- For trastuzumab IV weight-based dosing, three different weight scenarios were included based on adult female body weight data from the National Center for Health Statistics: 25:
- 25th percentile or first quartile (Q1): 62.2 kilograms (kg)
- 50th percentile or median: 73.1 kg
- 75th percentile or third quartile (Q3): 88.6 kg
- Weight-based doses were rounded up to the next drug reimbursement unit.
- Modeling scenarios (details of the following regimens and dosages by weight categories are specified in Table 1):
  - Scenario 1: trastuzumab monotherapy
    - One year of treatment
      - 52 weekly doses of trastuzumab-dkst and trastuzumab-IV
      - 18 doses every three weeks of trastuzumab-SC
    - Two years of treatment
      - 104 weekly doses of trastuzumab-dkst and trastuzumab-IV
      - 35 doses every three weeks of trastuzumab-SC
  - Scenario 2: trastuzumab-based therapy with pertuzumab and paclitaxel
    - One year of treatment: 18 doses every three weeks of trastuzumab-dkst, trastuzumab-IV, or trastuzumab-SC with pertuzumab (with paclitaxel in the initial cycle and maintenance cycles 2–4 only)
    - Two years of treatment: 35 doses every three weeks of trastuzumab-dkst, trastuzumab-IV, or trastuzumab-SC with pertuzumab (with paclitaxel in the initial cycle and maintenance cycles 2–4 only)
  - Two cost models were simulated for each scenario:
    - Costs of drugs only
    - Costs of drugs and drug administration
    - Treatment schedules are optimal with no missed or delayed cycles.
    - Administration frequency and duration are modeled per the approved label of all agents.
    - Costs not included in the model are:
      - Premedication or co-medication with analgesics, acetaminophen, antihistamine, glucocorticoids, or other medications (e.g., antiemetics):
        - Trastuzumab-dkst and reference trastuzumab-IV have similar safety profiles, hence, pre-/co-medications are assumed to be constant across both agents
        - Trastuzumab-SC may result in differential co-medication related to higher rates of hypersensitivity and anaphylactic reactions than trastuzumab-IV as reported in the prescribing information; this could favor trastuzumab-IV and trastuzumab-dkst but was not estimated due to limited real-world validation of incidence and treatment rates
      - Other agents in combination therapy (specifically, pertuzumab and paclitaxel) are constant across the models
      - Patient co-pay
      - Other patient costs, e.g., travel costs, time, etc.
      - Other indirect, opportunity, and intangible costs including patient comfort or preference
      - Incentives or rebates from manufacturers are considered confidential, variable, and undisclosed and therefore are not included; except that any incentives and rebates are assumed to be reflected in the average selling price (ASP).

### Cost inputs

- Drug costs utilized ASP for the 4th quarter of 2020 derived from 2nd quarter 2021 Centers for Medicare and Medicaid Services (CMS) Medicare Part B payment limits for marketed trastuzumab, pertuzumab, and paclitaxel:
  - Trastuzumab-dkst (10 mg): $56.63
  - Trastuzumab-IV (10 mg): $89.65
  - Trastuzumab-SC (10 mg): $69.20
  - Pertuzumab (1 mg): $12.46
  - Paclitaxel (1 mg): $0.18
- Drug administration costs were based on the 2020 Medicare Hospital Outpatient Prospective Payment reimbursement schedule for outpatient drug administration:
  - Chemotherapy IV infusion up to 1 h of single/initial drug: $309.56
  - Chemotherapy IV infusion of each additional drug up to 1 h: $60.46
  - Chemotherapy IV infusion each additional hour of the same/initial drug: $60.46
  - Chemotherapy SC injection: $60.46

### Analyses

This economic analysis utilized six discrete steps in the simulation modeling of cost-efficiency from conversion to biosimilar trastuzumab-dkst and budget-neutral expanded access afforded by those savings (see Figure 1). First, the per-label dosing schedule for each weight category (Q1, median, and Q3 weights) for both reference IV and SC trastuzumab formulations to biosimilar trastuzumab-dkst. The number-needed-to-convert (NNC) to purchase one additional dose of biosimilar trastuzumab-dkst was then estimated. NNC is defined as the number of patients that need to be converted to biosimilar trastuzumab-dkst treatment to purchase one additional unit treatment with trastuzumab-dkst monotherapy or trastuzumab-dkst in combination with pertuzumab and paclitaxel. The NNC was calculated as the ratio of treatment cost to the potential cost-savings generated by converting from reference trastuzumab.
IV or SC to biosimilar trastuzumab-dkst. Per-patient cost savings were then extrapolated to a panel of 1,000 patients with MBC. In each scenario, the cost savings were estimated for conversion rates ranging from 10% to 100%. Lastly, expanded access to trastuzumab-dkst was modeled based on the cost-savings generated in a panel of Q1-, median-, and Q3-weight patients to determine the number of single doses or 1-year regimens of trastuzumab-dkst monotherapy or in combination with pertuzumab and paclitaxel that could be purchased on a budget-neutral basis. The cost-savings, NNC and expanded access models were each conducted twice: once using drug cost only and once using costs for drug and drug administration.

Results

Cost savings from conversion to trastuzumab-dkst monotherapy

Cost of drug models

When considering only the cost of the drug, the per-patient savings over one year derived from conversion from trastuzumab-IV to trastuzumab-dkst monotherapy ranged from $22,721.89 in Q1-weight patients to $31,506.80 in Q3-weight patients (Table 2). The one-year cost-savings per patient from conversion from trastuzumab-SC to trastuzumab-dkst ranged from $20,712.77 in Q3-weight patients to $35,775.48 in Q1-weight patients (Table 2). Per-patient savings over two years are presented in Supplemental Table S1.

In a 1,000 patient-panel, conversion from reference trastuzumab-IV to trastuzumab-dkst for one year of monotherapy generates cost-savings ranging between $2,272,189 at 10% conversion rate in Q1-weight patients and $31,506,804 at 100% conversion rate in Q3-weight patients (Table 3). Conversion from trastuzumab-SC saves between $2,071,277 at a 10% conversion rate in Q3-weight patients and $35,775,475 at a 100% conversion rate in Q1-weight patients (Table 3). Savings over two years in a panel of 1,000 MBC patients are presented in Supplemental Table S2 (available online).

Cost of drug and administration models

Per-patient savings over one year from conversion from trastuzumab-IV to trastuzumab-dkst monotherapy, when taking both cost of drug and drug administration into account, ranged from $22,721.89 in Q1-weight patients to $31,506.80 in Q3-weight patients (Table 2). The cost-savings per patient from conversion from trastuzumab-SC to trastuzumab-dkst ranged from $5,643.47 in Q3-weight patients to $20,706.18 in Q1-weight patients (Table 2). Per-patient savings over two years are presented in Supplemental Table S1 (available online).

In a 1,000 patient-panel, conversion from reference trastuzumab-IV to trastuzumab-dkst for one year of monotherapy generates cost-savings ranging between $2,272,189 at 10% conversion rate in Q1-weight patients and $31,506,804 at 100% conversion rate in Q3-weight patients (Table 3). Conversion from trastuzumab-SC saves between $564,347 at a 10% conversion rate in Q3-weight patients and $20,706,175 at a 100% conversion rate in Q1-weight patients (Table 3).
Table 1. Trastuzumab dosing regimens and dosage by weight category for monotherapy and in combination with pertuzumab (and paclitaxel in cycles 1–4).

**Dosing regimens**

| Trastuzumab monotherapy | Dose Route Frequency | Maintenance cycle Dose Route Frequency |
|-------------------------|----------------------|---------------------------------------|
| Trastuzumab-dkst        | 4 mg/kg IV over 90 min Q1W | 2 mg/kg IV over 30 min Q1W |
| Trastuzumab IV          | 4 mg/kg IV over 90 min Q1W | 2 mg/kg IV over 30 min Q1W |
| Trastuzumab SC          | 600 mg SC over 5 min Q3W | 600 mg SC over 5 min Q3W |
| Trastuzumab in combination with pertuzumab (and paclitaxel in cycles 1–4) | Dose Route Frequency | Dose Route Frequency |
| Trastuzumab-dkst        | 8 mg/kg IV over 90 min Q3W | 6 mg/kg IV over 30 min Q3W |
| Trastuzumab IV          | 8 mg/kg IV over 90 min Q3W | 6 mg/kg IV over 30 min Q3W |
| Trastuzumab SC          | 600 mg SC over 5 min Q3W | 600 mg SC over 5 min Q3W |
| Pertuzumab              | 840 mg IV over 60 min Q3W | 420 mg IV over 30 min Q3W |
| Paclitaxel (cycles 1–4 only) | 175 mg/m² IV over 180 min Q3W | 175 mg/m² IV over 180 min Q3W |

**Dosage by weight category**

| Trastuzumab monotherapy | Initiation cycle | Maintenance cycle |
|-------------------------|-----------------|------------------|
| Q1 patient (62.2 kg)    | Q_3 patient (88.6 kg) |
| Q_1 patient (62.2 kg)   | Q_3 patient (88.6 kg) |
| Trastuzumab-dkst        | 248.8 mg 292.4 mg 354.4 mg | 124.4 mg 146.2 mg 177.2 mg |
| Trastuzumab IV          | 248.8 mg 292.4 mg 354.4 mg | 124.4 mg 146.2 mg 177.2 mg |
| Trastuzumab SC          | 600 mg 600 mg 600 mg | 600 mg 600 mg 600 mg |
| Trastuzumab in combination with pertuzumab (and paclitaxel in cycles 1–4) | Q_1 patient (62.2 kg) Median patient (73.1 kg) Q_3 patient (88.6 kg) |
| Q_1 patient (62.2 kg)   | Q_3 patient (88.6 kg) |
| Trastuzumab-dkst        | 497.6 mg 584.8 mg 708.8 mg | 337.2 mg 438.6 mg 531.7 mg |
| Trastuzumab IV          | 497.6 mg 584.8 mg 708.8 mg | 337.2 mg 438.6 mg 531.7 mg |
| Trastuzumab SC          | 600 mg 600 mg 600 mg | 600 mg 600 mg 600 mg |
| Pertuzumab              | 840 mg 840 mg 840 mg | 420 mg 420 mg 420 mg |
| Paclitaxel (cycles 1–4 only) | 237.5 mg 316.7 mg 395.9 mg | 237.5 mg 316.7 mg 395.9 mg |

**Abbreviations.** IV, intravenous; kg, kilogram; m², body surface area in meters height squared; mg, milligram; SC, subcutaneous; Q1W, every week; Q3W, every 3 weeks; Q1, first quartile (or 25th percentile); Q3, third quartile (or 75th percentile).**

**Cost savings from conversion to trastuzumab-dkst in combination with pertuzumab and paclitaxel**

**Cost of drug models**

When considering only the cost of the drug, per-patient savings for one year from conversion from trastuzumab-IV treatment to trastuzumab-dkst in combination with pertuzumab (all cycles) and paclitaxel (cycles 1–4) ranged from $22,986.10 in Q1-weight patients to $32,662.71 in Q3-weight patients (Table 2). The cost savings from conversion from trastuzumab-SC to trastuzumab-dkst ranged between $17,642.55 in Q1-weight patients and $34,234,181 at a conversion rate of 10% in Q3-weight patients (Table 2). Per-patient savings over two years are presented in Supplemental Table S1 (available online).

**Cost of drug and administration models**

When taking both costs of drug and drug administration into account, per-patient savings for one year from conversion from trastuzumab-IV treatment to trastuzumab-dkst in combination with pertuzumab (all cycles) and paclitaxel (cycles 1–4) ranged from $22,986.10 in Q1-weight patients to $32,662.71 in Q3-weight patients (Table 2). The cost savings from conversion from trastuzumab-SC to trastuzumab-dkst ranged between $17,642.55 in Q1-weight patients and $34,234,181 in Q3-weight patients (Table 2). Per-patient savings over two years are presented in Supplemental Table S1 (available online).

Extrapolated to a 1,000 patient-panel receiving trastuzumab in combination with pertuzumab (and paclitaxel in cycles 1–4), conversion from trastuzumab-IV saved between $2,298,610 at a conversion rate of 10% in Q1-weight patients and $32,662,714 at a conversion rate of 100% in Q3-weight patients (Table 4). Conversion from trastuzumab-SC generated cost savings that ranged between $1,764,255 at a conversion rate of 10% in Q1-weight patients and $34,234,181 at a conversion rate of 100% in Q3-weight patients (Table 4). Savings over two years in a panel of 1,000 MBC patients are presented in Supplemental Table S3 (available online).
Table 2. Per-patient costs and cost-savings over one year from conversion to trastuzumab-dkst.

### Trastuzumab monotherapy

| Costs per patient | Q1 patient (62.2 kg) | Median patient (73.1 kg) | Q3 patient (88.6 kg) |
|-------------------|----------------------|--------------------------|----------------------|
| Drug cost model   | trastuzumab-dkst     | trastuzumab IV           | trastuzumab SC       |
| Initiation cycle  | $1,415.67            | $2,241.32                | $4,151.93            |
| Each maintenance cycle | $736.15          | $1,165.49                | $4,151.93            |
| All cycles        | $38,959.18           | $61,681.07               | $74,734.66           |
| Cost-savings per patient from conversion | from trastuzumab IV to trastuzumab-dkst | $22,721.89 | $26,255.67 |
|                   | from trastuzumab SC to trastuzumab-dkst | $35,775.48 | $31,506.80 |

### Drug and drug administration cost model

| Costs per patient | Q1 patient (62.2 kg) | Median patient (73.1 kg) | Q3 patient (88.6 kg) |
|-------------------|----------------------|--------------------------|----------------------|
| Drug cost model   | trastuzumab-dkst     | trastuzumab IV           | trastuzumab SC       |
| Initiation cycle  | $1,785.69            | $2,611.34                | $4,212.39            |
| Each maintenance cycle | $1,045.71          | $1,475.05                | $4,212.39            |
| All cycles        | $55,116.76           | $77,838.65               | $75,822.94           |
| Cost-savings per patient from conversion | from trastuzumab IV to trastuzumab-dkst | $22,721.89 | $26,255.67 |
|                   | from trastuzumab SC to trastuzumab-dkst | $20,706.18 | $5,643.47 |

### Trastuzumab in combination with pertuzumab (and paclitaxel in cycles 1–4)

| Costs per patient | Q1 patient (62.2 kg) | Median patient (73.1 kg) | Q3 patient (88.6 kg) |
|-------------------|----------------------|--------------------------|----------------------|
| Drug cost model   | trastuzumab-dkst     | trastuzumab IV           | trastuzumab SC       |
| Initiation cycle  | $13,344.34           | $14,955.64               | $14,664.93           |
| Each maintenance cycle (with paclitaxel) | $7,429.96         | $8,684.95                | $9,430.07            |
| Each maintenance cycle (without paclitaxel) | $7,386.68        | $8,641.67                | $9,386.79            |
| All cycles        | $139,047.76          | $162,033.86              | $174,370.22          |
| Cost-savings per patient from conversion | from trastuzumab IV to trastuzumab-dkst | $22,986.10 | $26,651.98 |
|                   | from trastuzumab SC to trastuzumab-dkst | $35,322.46 | $32,662.71 |

### Drug and drug administration cost model

| Costs per patient | Q1 patient (62.2 kg) | Median patient (73.1 kg) | Q3 patient (88.6 kg) |
|-------------------|----------------------|--------------------------|----------------------|
| Drug cost model   | trastuzumab-dkst     | trastuzumab IV           | trastuzumab SC       |
| Initiation cycle  | $13,956.20           | $15,607.50               | $15,216.33           |
| Each maintenance cycle (with paclitaxel) | $8,041.82         | $9,296.81                | $9,981.47            |
| Each maintenance cycle (without paclitaxel) | $7,817.16        | $9,072.15                | $9,756.81            |
| All cycles        | $147,521.92          | $170,508.02              | $181,756.10          |
| Cost-savings per patient from conversion | from trastuzumab IV to trastuzumab-dkst | $22,986.10 | $26,651.98 |
|                   | from trastuzumab SC to trastuzumab-dkst | $34,232.46 | $32,662.71 |

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*Monotherapy maintenance cycles: weekly cycles for trastuzumab-dkst and trastuzumab-IV, every 3 weeks cycles for trastuzumab-SC.*

Abbreviations. IV, intravenous; SC, subcutaneous; Q1, first quartile (or 25th percentile); Q3, third quartile (or 75th percentile).
Table 3. Cost-savings from conversion to trastuzumab-dkst monotherapy over one year in a 1,000 patient-panel.

| Drug cost model | Conversion rate | Q1 patient (62.2 kg) | Median patient (73.1 kg) | Q3 patient (88.6 kg) |
|-----------------|-----------------|-----------------------|--------------------------|----------------------|
| Conversion from trastuzumab IV to trastuzumab-dkst | 100% | $22,721,888 | $26,255,670 | $31,506,804 |
| | 90% | $20,449,699 | $23,630,103 | $28,356,124 |
| | 80% | $18,177,510 | $21,004,536 | $25,205,443 |
| | 70% | $15,905,322 | $18,378,969 | $22,054,763 |
| | 60% | $13,633,133 | $15,753,402 | $19,094,082 |
| | 50% | $11,360,944 | $13,127,835 | $15,753,402 |
| | 40% | $9,088,755 | $10,502,268 | $12,602,722 |
| | 30% | $6,816,566 | $7,876,701 | $9,452,041 |
| | 20% | $4,544,378 | $5,231,134 | $6,301,361 |
| | 10% | $2,272,189 | $2,625,567 | $3,150,680 |
| Conversion from trastuzumab SC to trastuzumab-dkst | 100% | $35,775,475 | $29,716,416 | $20,712,768 |
| | 90% | $32,197,928 | $27,644,775 | $18,641,492 |
| | 80% | $28,620,380 | $23,773,133 | $16,570,215 |
| | 70% | $25,042,833 | $20,801,492 | $14,498,938 |
| | 60% | $21,465,285 | $17,929,850 | $12,427,661 |
| | 50% | $17,887,738 | $14,858,208 | $10,356,384 |
| | 40% | $14,310,190 | $11,886,567 | $8,285,107 |
| | 30% | $10,732,643 | $8,914,925 | $6,213,831 |
| | 20% | $7,155,095 | $5,943,283 | $4,142,554 |
| | 10% | $3,577,548 | $2,971,642 | $2,071,277 |

Table 4. Cost-savings from conversion to trastuzumab-dkst in combination with pertuzumab over one year in a 1,000 patient-panel.

| Drug cost model | Conversion rate | Q1 patient (62.2 kg) | Median patient (73.1 kg) | Q3 patient (88.6 kg) |
|-----------------|-----------------|-----------------------|--------------------------|----------------------|
| Conversion from trastuzumab IV to trastuzumab-dkst | 100% | $22,986,096 | $26,651,982 | $32,662,714 |
| | 90% | $20,687,486 | $23,986,784 | $29,366,443 |
| | 80% | $18,388,877 | $21,321,586 | $26,130,171 |
| | 70% | $16,090,267 | $18,656,387 | $22,863,900 |
| | 60% | $13,791,658 | $15,991,189 | $19,597,628 |
| | 50% | $11,493,048 | $13,325,991 | $16,331,357 |
| | 40% | $9,194,438 | $11,614,754 | $13,288,500 |
| | 30% | $7,895,829 | $9,795,595 | $10,659,210 |
| | 20% | $6,597,363 | $5,807,379 | $7,346,167 |
| | 10% | $4,323,246 | $2,903,690 | $1,873,083 |
| Conversion from trastuzumab SC to trastuzumab-dkst | 100% | $35,322,461 | $29,036,896 | $21,530,833 |
| | 90% | $31,790,215 | $26,333,206 | $16,857,750 |
| | 80% | $28,257,969 | $23,229,517 | $14,986,677 |
| | 70% | $24,725,723 | $20,325,827 | $13,111,383 |
| | 60% | $21,193,477 | $17,193,477 | $11,238,500 |
| | 50% | $17,661,231 | $14,518,448 | $9,365,417 |
| | 40% | $14,128,985 | $11,614,754 | $7,492,333 |
| | 30% | $10,596,738 | $8,711,069 | $5,619,250 |
| | 20% | $7,064,492 | $5,807,379 | $3,746,167 |
| | 10% | $3,532,246 | $2,903,690 | $1,873,083 |

Abbreviations. IV, intravenous; SC, subcutaneous; Q1, first quartile (or 25th percentile); Q3, third quartile (or 75th percentile).

**Number-needed-to-convert (NNC) in monotherapy**

**Cost of drug models**

When considering only the cost of the drug, the NNC from trastuzumab-IV to trastuzumab-dkst over one year of monotherapy to provide one additional dose of trastuzumab-dkst did not vary across weight categories and the NNC to provide a full year of monotherapy was 1.71 in all weight categories (Table 5). The NNC from trastuzumab-SC to trastuzumab-dkst to provide one additional dose was 0.02 in Q1-weight patients, 0.03 in median-weight patients, and 0.05 in Q3-weight patients. The NNC to provide a year of monotherapy ranged from 1.09 in Q1-weight patients to 2.61 in Q3-weight patients (Table 5).

**Cost of drug and administration models**

When taking both the cost of drug and drug administration into account, the NNC from trastuzumab-IV to trastuzumab-dkst over one year of monotherapy to provide one additional dose of trastuzumab-dkst was 0.05 in Q1-weight patients and 0.04 in median-weight and Q3-weight patients. The NNC to provide a full year of monotherapy ranged from 2.23 in Q3-weight patients to 2.43 in Q1-weight patients (Table 5). The NNC from trastuzumab-SC to trastuzumab-dkst to provide one additional dose was 0.05 in Q1-weight patients, 0.08 in median-weight patients, and 0.24 in Q3-weight patients. The NNC to provide a year of monotherapy ranged from 2.66 in Q1-weight patients to 12.44 in Q3-weight patients (Table 5).

**Abbreviations. IV, intravenous; SC, subcutaneous; Q1, first quartile (or 25th percentile); Q3, third quartile (or 75th percentile).**
Table 5. Number-needed-to-convert & expanded access from conversion to trastuzumab-dkst monotherapy.

| Conversion from | Drug cost model | Drug and drug administration cost model |
|-----------------|----------------|-----------------------------------------|
| trastuzumab-IV  |                |                                         |
| NNC to purchase 1 additional maintenance dose of trastuzumab-dkst | 0.03 | 0.04 |
| NNC to purchase 1 additional 1-year regimen of trastuzumab-dkst | 1.71 | 2.23 |
| Expanded access |                |                                         |
| Q1 patient (62.2 kg) | 0.03 | 0.04 |
| Median patient (73.1 kg) | 0.03 | 0.04 |
| Q3 patient (88.6 kg) | 0.05 | 0.04 |

| Conversion from | Number-needed-to-convert & expanded access from conversion to trastuzumab-dkst monotherapy. |
|-----------------|-----------------------------------------------------------------------------------------------|
| trastuzumab-SC  |                                                                                               |
| NNC to purchase 1 additional maintenance dose of trastuzumab-dkst | 0.02 | 0.08 | 0.24 |
| NNC to purchase 1 additional 1-year regimen of trastuzumab-dkst | 1.09 | 1.51 | 2.61 | 2.66 | 4.18 | 12.44 |
| Expanded access |                                                                                               |
| Q1 patient (62.2 kg) | 0.03 | 0.08 | 0.24 |
| Median patient (73.1 kg) | 0.05 | 0.05 | 0.08 |
| Q3 patient (88.6 kg) | 0.05 | 0.05 | 0.24 |

### Conversion from trastuzumab-IV

| Conversion rate | Number of additional maintenance doses | Number of additional 1-yr regimens |
|-----------------|----------------------------------------|------------------------------------|
| 100% | 30,866 | 583 |
| 90%  | 27,779 | 525 |
| 80%  | 24,693 | 467 |
| 70%  | 21,606 | 408 |
| 60%  | 18,520 | 350 |
| 50%  | 15,433 | 292 |
| 40%  | 12,346 | 233 |
| 30%  | 9,260  | 175 |
| 20%  | 6,173  | 117 |
| 10%  | 3,087  | 58  |

### Conversion from trastuzumab-SC

| Conversion rate | Number of additional maintenance doses | Number of additional 1-yr regimens |
|-----------------|----------------------------------------|------------------------------------|
| 100% | 48,598 | 918 |
| 90%  | 30,791 | 826 |
| 80%  | 27,369 | 735 |
| 70%  | 23,948 | 643 |
| 60%  | 20,527 | 551 |
| 50%  | 17,106 | 459 |
| 40%  | 13,685 | 367 |
| 30%  | 10,264 | 275 |
| 20%  | 6,842  | 184 |
| 10%  | 3,421  | 92  |

### Abbreviations

- NNC, number-needed-to-convert
- IV, intravenous
- SC, subcutaneous
- Q1, first quartile (or 25th percentile)
- Q3, third quartile (or 75th percentile)

**Cost savings derived from cost of drug only; expanded access to drug only.**

**Cost savings derived from cost of drug and drug administration; expanded access to drug and drug administration.**
**Number-needed-to-convert (NNC) in combination with pertuzumab**

**Cost of drug models**

When considering only the cost of the drug, the NNC from trastuzumab-IV to trastuzumab-dkst over one year of combination therapy with pertuzumab (and paclitaxel in cycles 1–4) to provide one additional dose of trastuzumab-dkst/pertuzumab was 0.25 in Q1-weight patients, 0.29 in median-weight patients, and 0.32 in Q1-weight patients (Table 6). The NNC to provide a full year of treatment with all agents ranged between 4.77 in Q2-weight patients to 6.05 in Q1-weight patients. The NNC from trastuzumab-SC to trastuzumab-dkst to provide one additional dose was 0.21 in Q1-weight, 0.27 in median-weight, and 0.44 in Q3-weight patients. The NNC to provide a year of combination therapy (all agents) ranged from 3.94 in Q1-weight patients to 8.32 in Q3-weight patients (Table 6).

**Cost of drug and administration models**

When taking both costs of drug and drug administration into account, the NNC from trastuzumab-IV to trastuzumab-dkst over one year of combination therapy with pertuzumab (and paclitaxel in cycles 1–4) to provide one additional dose of trastuzumab-dkst/pertuzumab was 0.27 in Q2-weight patients, 0.31 in median-weight patients, and 0.34 in Q1-weight patients (Table 6). The NNC to provide a full year of treatment with all agents ranged between 5.03 in Q3-weight patients to 6.42 in Q1-weight patients. The NNC from trastuzumab-SC to trastuzumab-dkst to provide one additional dose was 0.23 in Q1-weight, 0.29 in median-weight, and 0.49 in Q3-weight patients. The NNC to provide a year of combination therapy (all agents) ranged from 4.31 in Q1-weight patients to 9.31 in Q3-weight patients (Table 6).

**Expanded access from conversion to trastuzumab-dkst monotherapy**

**Cost of drug models**

When considering only the cost of the drug, the cost-savings generated from conversion from trastuzumab-IV to trastuzumab-dkst over one year of combination therapy with pertuzumab (and paclitaxel in cycles 1–4) to provide one additional dose of trastuzumab-dkst/pertuzumab was 0.25 in Q1-weight patients, 0.29 in median-weight patients, and 0.32 in Q1-weight patients (Table 5). The NNC to provide a full year of treatment with all agents ranged between 4.77 in Q2-weight patients to 6.05 in Q1-weight patients. The NNC from trastuzumab-SC to trastuzumab-dkst to provide one additional dose was 0.21 in Q1-weight, 0.27 in median-weight, and 0.44 in Q3-weight patients. The NNC to provide a year of combination therapy (all agents) ranged from 3.94 in Q1-weight patients to 8.32 in Q3-weight patients (Table 6).

**Cost of drug and administration models**

When taking both costs of drug and drug administration into account, the cost-savings generated from conversion from trastuzumab-IV to trastuzumab-dkst monotherapy at a rate of 100% in a panel of 1,000 patients with MBC could provide 21,729 additional maintenance doses of trastuzumab-dkst in Q1-weight patients, 22,654 in median-weight, and 23,710 in Q3-weight patients. Alternately, cost savings could provide a full 1-year regimen of weekly cycles of trastuzumab-dkst monotherapy to 412 Q1-weight, 429 median-weight, and 449 Q3-weight patients (Table 5).

Conversion from trastuzumab-SC at a conversion rate of 100% could provide 4,247 additional maintenance doses of trastuzumab-dkst or 80 1-year regimens in Q3-weight patients, 12,638 additional maintenance doses of trastuzumab-dkst or 239 1-year regimens in median-weight patients, and 19,801 doses or 376 1-year regimens in Q1-weight patients (Table 5).

**Expanded access to trastuzumab-dkst in combination with pertuzumab**

**Cost of drug models**

When considering only drug cost, cost-savings from 100% conversion from trastuzumab-IV in combination with pertuzumab in a panel of 1,000 MBC patients could provide 3,112 additional maintenance doses of trastuzumab-dkst/pertuzumab in Q1-weight, 3,449 in median-weight, and 3,939 in Q3-weight patients. Alternately, savings could provide a full year’s regimen (18 cycles of trastuzumab-dkst plus pertuzumab, with paclitaxel in cycles 1–4 only) to 165 Q1-weight, 183 median-weight, and 210 Q3-weight patients (Table 6).

Conversion from trastuzumab-SC at a conversion rate of 100% could provide 2,259 trastuzumab-dkst plus pertuzumab maintenance doses in Q3-weight patients, 3,758 doses in median-weight patients, and 4,782 doses in Q1-weight patients, or a full year’s regimen to 120, 200 and 254 patients, respectively (Table 6).

**Cost of drug and administration models**

When taking both cost of drug and drug administration into account, the cost-savings generated from conversion from trastuzumab-IV to trastuzumab-dkst in combination with pertuzumab in a panel of 1,000 patients with MBC could provide 21,729 additional maintenance doses of trastuzumab-dkst in Q1-weight patients, 22,654 in median-weight, and 23,710 in Q3-weight patients. Alternately, cost savings could provide a full 1-year regimen of weekly cycles of trastuzumab-dkst monotherapy to 412 Q1-weight, 429 median-weight, and 449 Q3-weight patients (Table 5).

Conversion from trastuzumab-SC at a conversion rate of 100% could provide 4,247 additional maintenance doses of trastuzumab-dkst or 80 1-year regimens in Q3-weight patients, 12,638 additional maintenance doses of trastuzumab-dkst or 239 1-year regimens in median-weight patients, and 19,801 doses or 376 1-year regimens in Q1-weight patients (Table 5).
Table 6. Number-needed-to-convert & expanded access from conversion to trastuzumab-dkst in combination with pertuzumab.

| Conversion from trastuzumab-IV | Drug cost model* | Drug and drug administration cost model** |
|-------------------------------|------------------|------------------------------------------|
| NNC to purchase 1 additional maintenance dose of trastuzumab-dkst and pertuzumab | Q<sub>1</sub> patient (62.2 kg) | Median patient (73.1 kg) | Q<sub>3</sub> patient (88.6 kg) | Q<sub>1</sub> patient (62.2 kg) | Median patient (73.1 kg) | Q<sub>3</sub> patient (88.6 kg) |
|                                | 0.32             | 0.29                                      | 0.25                                      | 0.34             | 0.31                                      | 0.27                                      |
| NNC to purchase 1 additional 1-year regimen of all agents (trastuzumab-dkst, pertuzumab, paclitaxel) for a new patient | 6.05             | 5.46                                      | 4.77                                      | 6.42             | 5.77                                      | 5.03                                      |

Expanded access

| Conversion from trastuzumab-IV | Q<sub>1</sub> patient (62.2 kg) | Median patient (73.1 kg) | Q<sub>3</sub> patient (88.6 kg) | Q<sub>1</sub> patient (62.2 kg) | Median patient (73.1 kg) | Q<sub>3</sub> patient (88.6 kg) |
|-------------------------------|----------------------------------|--------------------------|----------------------------------|--------------------------|--------------------------|----------------------------------|
| NNC to purchase 1 additional maintenance dose of trastuzumab-dkst | 0.21                            | 0.27                      | 0.44                             | 0.23                     | 0.29                      | 0.49                             |
| NNC to purchase 1 additional 1-year regimen of all agents (trastuzumab-dkst, pertuzumab, paclitaxel) for a new patient | 3.94                            | 5.01                      | 8.32                             | 4.31                     | 5.51                      | 9.31                             |

Conversion rate

| Conversion from trastuzumab-IV | Number of additional maintenance doses | Number of additional 1-yr regimens | Number of additional maintenance doses | Number of additional 1-yr regimens | Number of additional maintenance doses | Number of additional 1-yr regimens | Number of additional maintenance doses | Number of additional 1-yr regimens |
|-------------------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|
| 100%                          | 3,112                                 | 165                               | 3,449                                 | 183                               | 3,939                                 | 210                               | 2,940                                 | 156                               |
| 90%                           | 2,801                                 | 149                               | 3,105                                 | 165                               | 3,545                                 | 189                               | 2,646                                 | 140                               |
| 80%                           | 2,489                                 | 132                               | 2,760                                 | 147                               | 3,151                                 | 168                               | 2,352                                 | 125                               |
| 70%                           | 2,178                                 | 116                               | 2,415                                 | 128                               | 2,757                                 | 147                               | 2,058                                 | 109                               |
| 60%                           | 1,867                                 | 99                                | 2,070                                 | 110                               | 2,363                                 | 126                               | 1,764                                 | 93                                |
| 50%                           | 1,556                                 | 83                                | 1,725                                 | 92                                | 1,969                                 | 105                               | 1,470                                 | 78                                |
| 40%                           | 1,245                                 | 66                                | 1,380                                 | 73                                | 1,575                                 | 84                                | 1,176                                 | 62                                |
| 30%                           | 934                                  | 50                                | 1,035                                 | 55                                | 1,182                                 | 63                                | 882                                  | 47                                |
| 20%                           | 622                                  | 33                                | 690                                  | 37                                | 788                                  | 42                                | 588                                  | 31                                |
| 10%                           | 311                                  | 17                                | 345                                  | 18                                | 394                                  | 21                                | 294                                  | 16                                |

| Conversion from trastuzumab-IV | Number of additional maintenance doses | Number of additional 1-yr regimens | Number of additional maintenance doses | Number of additional 1-yr regimens | Number of additional maintenance doses | Number of additional 1-yr regimens | Number of additional maintenance doses | Number of additional 1-yr regimens |
|-------------------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|
| 100%                          | 4,782                                 | 254                               | 3,758                                 | 200                               | 2,259                                 | 120                               | 4,379                                 | 232                               |
| 90%                           | 4,304                                 | 229                               | 3,382                                 | 180                               | 2,033                                 | 108                               | 3,941                                 | 209                               |
| 80%                           | 3,826                                 | 203                               | 3,006                                 | 160                               | 1,807                                 | 96                                | 3,503                                 | 186                               |
| 70%                           | 3,347                                 | 178                               | 2,631                                 | 140                               | 1,581                                 | 84                                | 3,066                                 | 162                               |
| 60%                           | 2,869                                 | 152                               | 2,255                                 | 120                               | 1,355                                 | 72                                | 2,628                                 | 139                               |
| 50%                           | 2,391                                 | 127                               | 1,879                                 | 100                               | 1,129                                 | 60                                | 2,190                                 | 116                               |
| 40%                           | 1,913                                 | 102                               | 1,503                                 | 80                                | 903                                  | 48                                | 1,752                                 | 93                                |
| 30%                           | 1,435                                 | 76                                | 1,127                                 | 60                                | 678                                  | 36                                | 1,314                                 | 70                                |
| 20%                           | 956                                  | 51                                | 752                                  | 40                                | 452                                  | 24                                | 876                                  | 46                                |
| 10%                           | 478                                  | 25                                | 376                                  | 20                                | 226                                  | 12                                | 438                                  | 23                                |

| Conversion from trastuzumab-IV | Number of additional maintenance doses | Number of additional 1-yr regimens | Number of additional maintenance doses | Number of additional 1-yr regimens | Number of additional maintenance doses | Number of additional 1-yr regimens | Number of additional maintenance doses | Number of additional 1-yr regimens |
|-------------------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|
| 100%                          | 4,782                                 | 254                               | 3,758                                 | 200                               | 2,259                                 | 120                               | 4,379                                 | 232                               |
| 90%                           | 4,304                                 | 229                               | 3,382                                 | 180                               | 2,033                                 | 108                               | 3,941                                 | 209                               |
| 80%                           | 3,826                                 | 203                               | 3,006                                 | 160                               | 1,807                                 | 96                                | 3,503                                 | 186                               |
| 70%                           | 3,347                                 | 178                               | 2,631                                 | 140                               | 1,581                                 | 84                                | 3,066                                 | 162                               |
| 60%                           | 2,869                                 | 152                               | 2,255                                 | 120                               | 1,355                                 | 72                                | 2,628                                 | 139                               |
| 50%                           | 2,391                                 | 127                               | 1,879                                 | 100                               | 1,129                                 | 60                                | 2,190                                 | 116                               |
| 40%                           | 1,913                                 | 102                               | 1,503                                 | 80                                | 903                                  | 48                                | 1,752                                 | 93                                |
| 30%                           | 1,435                                 | 76                                | 1,127                                 | 60                                | 678                                  | 36                                | 1,314                                 | 70                                |
| 20%                           | 956                                  | 51                                | 752                                  | 40                                | 452                                  | 24                                | 876                                  | 46                                |
| 10%                           | 478                                  | 25                                | 376                                  | 20                                | 226                                  | 12                                | 438                                  | 23                                |

Abbreviations. NNC, number-needed-to-convert; IV, intravenous; SC, subcutaneous; Q<sub>1</sub>, first quartile (or 25<sup>th</sup> percentile); Q<sub>3</sub>, third quartile (or 75<sup>th</sup> percentile).

*Cost savings derived from cost of drug only; expanded access to drug only.

**Cost savings derived from cost of drug and drug administration; expanded access to drug and drug administration.
Discussion

The cost-efficiency and expanded access simulations reported here are the first such analyses for a therapeutic biosimilar agent in the US and extend similar studies in supportive cancer care. The principal findings of the present simulations are five-fold. First, conversion from trastuzumab-IV to trastuzumab-dkst could reduce the drug cost of monotherapy by 37% in all patient weight categories. In a panel of 1,000 MBC patients this could generate cost savings up to $31.5 million in Q1-weight patients in one year of treatment. Second, conversion from trastuzumab-SC to trastuzumab-dkst monotherapy is also cost-efficient in all patients with a reduction in drug costs of 48% in Q1-weight, 40% in median-weight and 28% in Q3-weight patients which could generate up to $35.8 million in savings in one year. When taking the cost of drug and drug administration into account, savings from conversion from trastuzumab-SC remain at 27% in Q1-weight, 19% in median-weight and 7% in Q3-weight patients which could generate up to $20.7 million in savings in one year. Third, in combination with pertuzumab, the conversion from reference IV and SC trastuzumab formulations to trastuzumab-dkst are cost-efficient in all patients with savings of 13% (Q1-weight patients) to 17% (Q3-weight patients) versus trastuzumab-IV and savings of 10% (Q3-weight patients) to 19% (Q1-weight patients) versus trastuzumab-SC. Under these scenarios, the savings in a panel of 1,000 MBC patients could reach $32.7 million in one year for the conversion from trastuzumab-IV in Q1-weight patients and $34.2 million for conversion from trastuzumab-SC in Q1-weight patients. Fourth, the number of patients needed to convert to trastuzumab-dkst monotherapy in order to purchase a full year of treatment for an additional patient on a budget-neutral basis is low: less than two patients when converted from trastuzumab-IV and between 1.09 in Q1-weight patients and 2.61 in Q3-weight patients converted from trastuzumab-SC. The NNC to trastuzumab-dkst in combination with pertuzumab to purchase a full year of treatment with all agents for an additional patient ranges from 4.77 (Q1-weight) to 6.05 (Q1-weight) when converted from trastuzumab-IV and from 3.94 (Q1-weight) to 8.32 (Q3-weight) from trastuzumab-SC. Fifth, these cost-savings and low NNCs translate into potential expanded access to additional doses of trastuzumab-dkst monotherapy in excess of 30,000 doses or a full year of treatment to more than 583 additional patients on a budget-neutral basis. In combination with pertuzumab, savings could provide up to 3,900 maintenance trastuzumab-dkst/pertuzumab doses or a full year of treatment to 210 additional patients (trastuzumab-dkst/pertuzumab/paclitaxel).

Patients with MBC vary in pre-morbid body composition and the cancer itself may further affect weight. With trastuzumab, pertuzumab, and paclitaxel IV dosing based on body weight or body surface area, a notable feature of our model is that it was not limited to one weight/BSA (e.g. mean or median) but instead considered three different patient weight scenarios to better reflect real-life variation in MCB patients and enhance the ecological validity of the findings. Trastuzumab-dkst was cost-efficient versus trastuzumab-IV and trastuzumab-SC in both monotherapy and combination therapy with pertuzumab in all three weight categories. Versus trastuzumab-IV, per-patient cost-savings increased with each weight category in both monotherapy and combination therapy. Versus trastuzumab-SC, cost savings declined with each increasing weight category in both monotherapy and combination therapy. This was attributable to dosing for trastuzumab-dkst being weight-based but fixed for trastuzumab-SC.

In our models of drug and drug administration costs, the per-patient cost-savings over trastuzumab-SC for 1 year of monotherapy are smaller than the savings for 1 year of combination therapy because of the drug administration costs. The administration cost for 1 year of trastuzumab monotherapy IV formulations is $15,069 higher than the cost for SC administration while the drug administration costs for 1 year of IV trastuzumab formulations in combination with pertuzumab is only $1,088 higher than SC administration. This is due to two factors. First, trastuzumab monotherapy is administered weekly if IV but every 3 weeks if SC. In contrast, trastuzumab in combination with pertuzumab is administered every 3 weeks regardless of route of administration. Secondly, pertuzumab is administered IV regardless of trastuzumab route of administration. Hence, the substantial difference in the drug cost between biosimilar trastuzumab-dkst and trastuzumab-SC for 1 year of monotherapy not only eliminates the difference in the administration costs but actually affords cost-savings over trastuzumab-SC in all weight categories. Savings over trastuzumab-SC are even larger in combination therapy with pertuzumab.

This first cost-efficiency and expanded access analysis on conversion to therapeutic biosimilars is consistent with prior investigations in the supportive cancer care settings. Recent real-world evidence has corroborated the findings of those economic modeling studies in supportive care and underscore the need to re-assess the cost-efficiency of biosimilar conversion in the therapeutic cancer care setting once such data accrue in both quality and volume. Further, the present findings are aligned with a recent “world-with vs. world-without” incidence-based budget impact analysis with a 5-year time horizon of introducing the trastuzumab biosimilar Herzuma in the EU-5 countries (UK, France, Germany, Spain, Italy). Though different in objective, methodology, and data and therefore not directly comparable to our cost-efficiency analysis, it demonstrated potential budget savings of €19 million to €172 million and expanded treatment to 622 to 3,688 more patients.

In the US, Russell and colleagues assessed the total healthcare costs associated with HER2-positive MBC care in the US using claims data from 2011 to 2017. They estimated median 1-year costs to be $194,527 and median 3-year costs to be $319,197 per patient. Extrapolated to the HER2-positive MBC population in the US, the aggregate 3-year cost of treatment was $3-4 billion annually of which 43% is for HER2-targeted treatment. If trastuzumab-dkst were adopted, the costs of HER2-targeted treatment could be reduced by ~30% over trastuzumab-IV monotherapy and by up to 19% over trastuzumab-SC in combination with pertuzumab.
The cost implications of biosimilar conversion are particularly relevant in light of cost-containment initiatives in cancer care. For example, CMS developed the Oncology Care Model (OCM) to promote value-based care programs to replace the fee-for-service reimbursement models with the ultimate goal of controlling the rise in cancer treatment costs. The OCM, which was launched in 2016, and its successor, the Oncology Care First Model, aim to reward practices for delivering high-value cancer care while containing cost. Recent studies demonstrated that, in the supportive cancer care setting, biosimilar pegfilgrastim products can be successfully implemented within the OCM model resulting in significant cost savings to CMS and significant improvement in financial outcomes for participating practices. In addition, as we showed recently, biosimilar conversion not only provides cancer care providers operating under the OCM model with savings, thus improving drug cost metrics, but these savings can be applied to patient-centric services such as nutrition or transportation support and therefore benefit economically disadvantaged patients.

The global availability of biosimilars continues to expand and this should be endorsed from a global health perspective. Biosimilars offer a cost-responsible trajectory to assuring access to otherwise expensive anticancer biologics worldwide, especially in low-income, low-middle income, and middle-income countries. In 2019, the World Health Organization (WHO) included the biosimilars of rituximab and trastuzumab in the WHO List of Essential Medicines. Arguably, biosimilars approved in well-regulated markets (and therefore regulatorily assured to be equivalently effective and safe) should be recognized internationally as cost-responsible and affordable ways of expanding access to supportive and therapeutic cancer care in economically constrained countries. A recent budget impact analysis of the conversion to biosimilar rituximab in the Middle East and North Africa (MENA) region revealed that the projected savings that will result from the uptake of biosimilar rituximab were estimated to be about $47 million and across 13 countries included in the study, the saving will expand access to rituximab therapy to 6,589 patients, which is equivalent to 14% increase in access. Relatedly, the cost of reference trastuzumab represents a key barrier to treating HER2-positive MBC patients in Latin America. The cost-efficiency of trastuzumab-dkst presented here demonstrates an actionable option for low- and middle-income countries in overcoming disparities in access to reference anti-HER2 biologics while also enabling more patients to be treated.

Our study has several strengths, some limitations, while also suggesting areas of future research. Driven in part by the dosing requirements of trastuzumab, we performed weight-stratified analyses to establish that regimens using trastuzumab-dkst save costs and enable budget-neutral expanded access across the regimens, weight categories, and 1-year and 2-year treatment duration. Thus our findings make both the clinical and the business case for treating HER2-positive patients with MBC with trastuzumab-dkst. At this time, the analyses are simulations and it will be imperative to replicate the study once real-world utilization and outcomes data are available. We applied the 4th quarter 2020 ASP as cost inputs. As this price varies from quarter to quarter, our results need to be monitored as the ASP of the treatment agents evolves. Our analyses should be replicated for other trastuzumab biosimilars and repeated as biosimilar trastuzumab-SC formulations are approved. Referring back to the assumptions section of this paper, several costs were not included in this model such as costs of transportation and time to reach the infusion center, chair time and associated infusion staff costs, as well as intangible costs related to patient preference and convenience. This was because these costs are independent of and therefore constant regardless of whether reference product or biosimilar are considered – though administration route may exert an effect. The impact of clinician acceptance of biosimilars, their potential concerns about effectiveness or safety, should be kept in mind, including a possible nocebo effect. Our analyses did not consider interruptions to or discontinuation of chemotherapy due to treatment-related adverse events and toxicities, and therefore consider an all-patients-prophylactically best-case scenario. As more real-world data emerge, a better sense of real-world variability in the parameters of interest may inform sensitivity analyses, which in turn may inform pricing dynamics.

Conclusions
This economic simulation demonstrates that biosimilar trastuzumab-dkst is cost-efficient over trastuzumab-IV and trastuzumab-SC across all patient weights in both monotherapy and in combination with pertuzumab and paclitaxel. Only two patients needed to be converted from reference to biosimilar agent to purchase a full year of trastuzumab-dkst monotherapy and less than three patients to purchase a full year of trastuzumab-dkst in combination with pertuzumab and paclitaxel. The marked cost-savings achieved by biosimilar conversion to trastuzumab-dkst can be re-allocated to provide expanded access to additional doses or year-long regimens of trastuzumab-dkst on a budget-neutral basis.

Notes
i. Herceptin is a registered trademark of Genentech, South San Francisco, CA, USA.
ii. Ogivri is a registered trademark of Viatris, Cannonsburg, PA, USA.
iii. Herceptin Hylecta is a registered trademark of Genentech, South San Francisco, CA, USA.
iv. Perjeta is a registered trademark of Genentech, South San Francisco, CA, USA.
v. Herzuma is a registered trademark of Celltrion, Incheon, Korea.

Transparency
Declaration of funding
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Declaration of financial/other interests
AM has been a speaker and consultant for Pfizer, Coherus, and Viatris.
KM and IA are equity shareholders of Matrix45, LLC and, by company policy, are prohibited from owning equity in client organizations (except through mutual funds or other independently administered collective investment instruments) or contracting independently with client organizations. Matrix45 provides similar services to those described in this article to other biopharmaceutical companies on a non-exclusivity basis. AFA is an employee of Viatris. IA is the Deputy Editor-in-Chief of the Journal of Medical Economics and was not involved in the editorial processing or decisions related to this manuscript.

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**Author contributions**

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