



# White Paper on the Value of Time Savings for Patients and Healthcare Providers of Breast Cancer Therapy: The Fixed-Dose Combination of Pertuzumab and Trastuzumab for Subcutaneous Injection as an Example

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## ABSTRACT

Health technology assessments and value frameworks are becoming increasingly important for clinical decision-making. Most of these frameworks, however, focus on value to payers rather than patients and healthcare providers and may ignore other sources of economic value such as patient and physician time cost, impact on productivity, and direct health system costs. This article focusses on fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection (PH FDC SC) in the treatment of HER2-positive breast cancer. We review relevant clinical evidence, examine data on time and resource use of the subcutaneous administration of trastuzumab compared with intravenous treatment and how it can be

extrapolated to PH FDC SC, and discuss the value PH FDC SC can bring to patients and healthcare providers. We will also provide our own experiences of PH FDC SC from the healthcare (oncologist, healthcare economist, pharmacist) and patient point of view. The data, combined with our personal experiences, suggest that switching from intravenous pertuzumab and trastuzumab to PH FDC SC could reduce non-drug costs for healthcare providers treating patients with HER2-positive breast cancer through time savings and other economic benefits. Furthermore, PH FDC SC could also save patient time given its shorter administration and post-injection observation time versus intravenous infusions, potentially resulting in reduced productivity loss. These benefits could be applied to other subcutaneous formulations, either currently available or in development.

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## PLAIN LANGUAGE SUMMARY

New therapies are increasingly assessed by looking at their value to those who pay for them rather than their value to patients and healthcare providers. Value assessments conducted from the payers' perspective often ignore such things as patient and healthcare system time and costs. The fixed-dose combination of

pertuzumab and trastuzumab for subcutaneous injection (also known as pertuzumab, trastuzumab, and hyaluronidase-zzxf, abbreviated to PH FDC SC), is injected under the skin to treat a subtype of breast cancer called HER2-positive breast cancer. PH FDC SC is as effective as pertuzumab and trastuzumab, which are infused separately into a vein, but takes a lot less time to administer to patients. This transition is similar to what was seen when a subcutaneous version of trastuzumab was developed and compared to the intravenous original. Also, subcutaneous trastuzumab reduced costs associated with treating patients compared with intravenous infusions. The same benefits of PH FDC SC to patients and healthcare providers can be expected, and our personal experiences as an oncologist, healthcare economist, patient, and pharmacist agree. PH FDC SC could save patient and healthcare provider time given its shorter injection and observation times versus intravenous infusions, potentially resulting in better productivity for these people and a smaller cost to healthcare providers. These benefits could be applied to other subcutaneous formulations, either currently available or in development.

**Keywords:** Costs; Fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection; HER2-positive breast cancer; Pertuzumab, trastuzumab, and hyaluronidase-zzxf

### Key Summary Points

The fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection for the treatment of HER2-positive breast cancer has shorter administration and observation times than intravenous pertuzumab and trastuzumab infusions

The fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection offers substantial potential for non-drug cost savings for healthcare providers, akin to those seen with subcutaneous trastuzumab versus intravenous trastuzumab

From the experiences of healthcare and patient authors, switching from intravenous pertuzumab and trastuzumab to the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection is preferred by patients due to time savings having a positive impact on daily life; generates cost savings; releases capacity in chemotherapy units for other treatments; significantly reduces intravenous compounding costs; offers flexibility in terms of scheduling and care (patients can switch between intravenous and subcutaneous methods as needed); and reduces wastage

These benefits could be applied to other subcutaneous formulations, either currently available or in development

## DIGITAL FEATURES

This article is published with digital features, including an infographic, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.16989670>.

## INTRODUCTION

Health technology assessments and value frameworks (e.g., those of the National Comprehensive Cancer Network, the Institute for Clinical and Economic Review, and the American Society of Clinical Oncology in the US, and the National Institute for Health and Care Excellence in the UK) are becoming increasingly important for clinical decision-making. Most of

these frameworks, however, focus on value to payers rather than patients and healthcare providers and may ignore other sources of economic value such as patient and physician time cost, impact on productivity, and direct health system costs. To apply this broader approach to measuring treatment value to patients and physicians, we reviewed the current clinical and economic evidence on a recently approved treatment for HER2-positive breast cancer. In particular, we examined broader value components of a ready-to-use fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection (pertuzumab, trastuzumab, and hyaluronidase-zzxf; PH FDC SC). This treatment has been approved by the US Food and Drug Administration [1] and the European Medicines Agency [2] for HER2-positive early and metastatic breast cancer, as an alternative to separate intravenous (IV) pertuzumab and trastuzumab infusions. This formulation offers patients faster, more convenient, and less invasive treatment than IV infusions [3].

PH FDC SC has identical active ingredients to pertuzumab and trastuzumab, containing 1200 mg pertuzumab plus 600 mg trastuzumab in a fixed, non-weight-based loading dose of 15 ml as a starting dose, and fixed, non-weight-based maintenance doses of 600 mg pertuzumab plus 600 mg trastuzumab in 10 ml. PH FDC SC also contains 2000 U/ml of the permeation enhancer, recombinant human hyaluronidase. Fixed doses are utilized with P IV infusions and H SC injections, whereas H IV infusions are administered according to the patient's body weight.

PH FDC SC has much shorter administration and observation times than IV pertuzumab and trastuzumab [1, 2, 4–7]; a comparison is shown in Fig. 1.

### Compliance with ethics guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

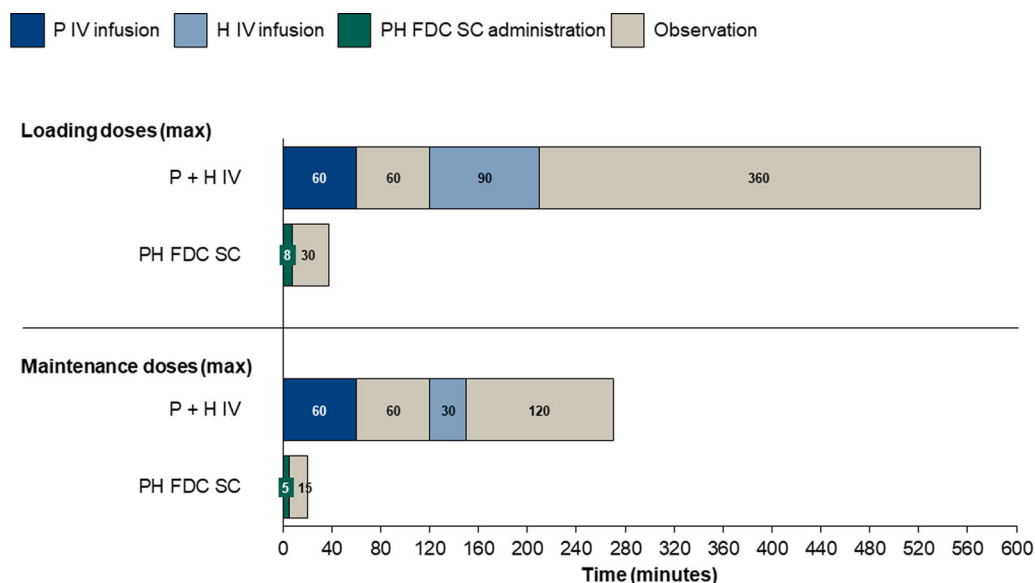
## VALUE OF PH FDC SC TO PATIENTS AND HEALTHCARE PROFESSIONALS

### Key Clinical Trial Data

PH FDC SC approvals for the treatment of HER2-positive breast cancer are based on results from two key clinical trials. First, the pivotal Phase 3 FeDeriCa study compared the pharmacokinetics, efficacy, and safety of PH FDC SC and IV pertuzumab and trastuzumab in 500 patients with HER2-positive early breast cancer in the neoadjuvant-adjuvant setting [3, 8]. In the neoadjuvant phase of the study, patients also received one of two protocol-approved standard chemotherapy regimens, and the primary analysis from this phase showed that PH FDC SC was non-inferior to IV pertuzumab and trastuzumab in terms of cycle 7 (pre-dose cycle 8) pertuzumab serum  $C_{\text{trough}}$  concentrations [3]. PH FDC SC and IV pertuzumab and trastuzumab also had comparable total pathologic complete response rates and similar safety profiles [3].

During the adjuvant phase of the study, where patients received HER2-targeted therapy only, safety remained comparable (with the exception of adverse events associated with the different routes of administration, i.e., infusion-/administration-related reactions within 24 h; all were grade 1/2 and mostly due to local injection site reactions associated with SC administration) and data confirmed the expectation that most adverse events are observed during concomitant chemotherapy [8].

The second clinical trial, the Phase 2 PHranceSCa study, assessed patients' preferences, via questionnaire, for PH FDC SC or IV pertuzumab and trastuzumab after experiencing both administration methods post-surgery, following completion of neoadjuvant IV pertuzumab, trastuzumab, and chemotherapy [9]. Patients were randomized 1:1 to receive IV pertuzumab and trastuzumab for cycles 1–3, followed by PH FDC SC for cycles 4–6, or vice versa. Patients could then choose SC or IV to continue up to 18 cycles. The primary analysis showed that most patients strongly preferred PH FDC SC (85.0% overall vs. 13.8% for IV



**Fig. 1** Comparison of maximum administration and observation times for IV P + H, and PH FDC SC, according to local labels [1, 2, 4–7]. *H* trastuzumab, *IV* intravenous, *P* pertuzumab, *PH FDC SC* fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection. Intravenous pertuzumab and trastuzumab can be given in any order. The 15-min PH FDC SC maintenance dose observation period assumes that the loading dose injection was well tolerated; patients could be observed for longer at the discretion of the investigator, per

pertuzumab and trastuzumab; 1.3% had no preference). The two primary reasons patients preferred PH FDC SC were that: (1) they spent less time in the clinic (42.2%) and (2) they were more comfortable during administration (25.9%). In fact, 86.9% of patients chose to continue their adjuvant HER2-targeted therapy with PH FDC SC rather than IV pertuzumab and trastuzumab (13.1%). PHranceSCa also assessed, again via questionnaire, healthcare professionals' (HCPs) perceptions of the different routes of administration, and these HCPs perceived that PH FDC SC required less time in the drug preparation room (5 min vs. 15–20 min depending on the treatment cycle, respectively) and the treatment room than IV pertuzumab and trastuzumab (7–8 min vs. 60–150 min, respectively). Furthermore, 80.0% agreed or strongly agreed that staff time associated with preparation procedures would be reduced in the

local requirements. Administration/observation times vary according to local labels. IV trastuzumab observation times are European Union times. Reprinted from *Lancet Oncology* [22], Tan AR, et al., Fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection plus chemotherapy in HER2-positive early breast cancer (FeDeriCa): a randomised, open-label, multicentre, non-inferiority, phase 3 study, p 85–97, Copyright (2021), with permission from Elsevier

drug preparation room. In the treatment room, 95.6% of HCPs agreed or strongly agreed that there was less time from start of preparation to finish of administration with PH FDC SC; 86.2%, that less resource was needed for administration; 86.8%, that PH FDC SC was more convenient for patients; and 79.2%, that PH FDC SC was better for care optimization within their treatment site [10]. These time-saving benefits were not at the cost of HCP interaction time [9].

PH FDC SC was generally well tolerated, with no new safety signals (even when switching) [9].

## Time Savings With Subcutaneous Versus Intravenous Administration of Trastuzumab Could Be Extrapolated to PH FDC SC

While the above data on HCP time savings are based on perceptions, a number of observational studies have shown that the SC injection of therapeutics can save patients' and healthcare providers' time compared with the equivalent IV infusion, in both clinical trial and real-world settings. Specifically, a time-and-motion study ran alongside the PrefHer clinical trial, which was designed in a similar way to PHranceSCa, and demonstrated important reductions in patient chair time and active HCP time across eight countries [11]. This time-and-motion assessment showed that, per treatment session, SC administration via a hand-held syringe (comparable to a single-use injection device) reduced patient chair time (time between entry and exit of the infusion chair) versus IV infusion by a mean of 55.2 min (mean time saving range across countries: 40.3–80.6 min;  $p < 0.0001$ ). Over a standard 18-cycle course of treatment for HER2-positive early breast cancer, this would equate to 16.3 h of time saved (range across countries: 9.3–23.5 h). Furthermore, active HCP time, defined as time actively dedicated by any staff member to prespecified tasks associated with SC injections/IV infusions, was reduced by a mean of 17.0 min (range: 5.1–28.0 min;  $p < 0.0001$ ) per treatment session. Over the 18-cycle standard treatment course, this equated to a mean reduction of 1.6–8.4 h. This time reduction was mainly driven by a reduction in nursing staff time, due to fewer tasks being performed in the drug preparation area, and no installation or disconnection of peripheral catheters (or no permanent line flushing, if indicated). However, it should be noted that although patient chair time was longer for the IV infusions compared with the SC injection, the active HCP time during the IV infusions (the time needed to start the actual infusion process and monitor the patient during the infusion) was shorter than the active HCP time during the SC injections. In addition, potential differences in observation times (beyond the monitoring during infusion/injection

and subsequent immediate monitoring) were not taken into consideration, meaning that estimations were conservative.

Evidence that SC administration reduces administration times compared with IV was initially gained from the pivotal HannaH study [12] and then the time-and-motion study assessment performed alongside PrefHer [11] (both clinical trial settings). However, a number of independent observational studies (some of them retrospective) have since been reported that show that time savings for patients and healthcare providers due to shorter SC administration times can be replicated in real-world settings [13–17]. Similar time savings are likely to be found in PH FDC SC as well, relative to IV modes of administration (even more so in fact, as PH FDC SC effectively replaces two IV administrations instead of one). Although data on this are not yet available in the literature, we have experienced this first-hand (see our experiences below). As mentioned above, the ready-to-use fixed-dose combination does not require reconstitution as does IV trastuzumab and has much-reduced preparation, administration, and observation times versus IV pertuzumab and trastuzumab. Hence, patient chair time and active HCP time would be expected to be significantly reduced with PH FDC SC, which might lead to reduced healthcare provider/system costs. Reduced patient hospital time is also advantageous during the COVID-19 pandemic; not only may the risk of SARS-CoV-2 infection increase, but also patients with solid (or hematologic) malignancies and SARS-CoV-2 infection are at a high risk of mortality [18]. An ongoing time-and-motion study of PH FDC SC for HER2-positive early breast cancer (EudraCT Number: 2020-004241-36) will provide more insight into PH FDC SC time savings.

### Economic Translation of Time Savings to Cost Savings With PH FDC SC

Although costs associated with the time savings listed above were not captured in the global PrefHer time-and-motion sub-study (some regional PrefHer time-and-motion sub-studies, e.g., the UK [19], showed how H SC reductions

in administration time were reflected in reduced costs), there is supplementary evidence on costs associated with the administration of H IV and H SC. In this section we will discuss data from the literature on sources of savings beyond time alone. Several studies report that costs for non-drug consumables can further reduce overall costs associated with H SC injection compared with IV infusion [13, 16, 20, 21]. Moreover, a Swedish study [15] reported significant H SC central venous access device (CVAD)-related cost savings, i.e., direct monetary cost savings from avoiding the need for surgery to implant port-a-caths, which can be otherwise required for patients newly diagnosed with early breast cancer and receiving IV infusions.

A recent model-based cost-minimization analysis [22] used the PrefHer time-and-motion study data [11] and further evidence on SC- and IV-related costs [13–15, 20, 23, 24] to estimate potential mean non-drug cost differences between PH FDC SC and IV pertuzumab and trastuzumab per patient over the standard 18-cycle course in Western Europe and the USA. For Western Europe, the authors considered both costs derived from PH FDC SC and IV pertuzumab and trastuzumab preparation and administration times (such as the costs for patient chair time and HCP time) and cost elements unrelated to time, such as the cost of non-drug consumables. A base case scenario assumed PH FDC SC patient chair and active HCP times were equal to the corresponding H SC pooled outcomes of the PrefHer time-and-motion study for the hand-held syringe and used the H IV pooled results to extrapolate IV pertuzumab and trastuzumab times. This extrapolation of patient chair and active HCP times (from one IV infusion to two) multiplied PrefHer time-and-motion H IV times by a factor smaller than two, as the authors assumed a gain of efficiencies (e.g., venous catheter installation/line flushing) when two IV infusions are administered sequentially. Two supplementary scenarios varied these and other relevant assumptions regarding potential differences in real-world and clinical trial settings times, cost of non-drug consumables, chair time unit costs, CVAD implantations and costs, and patient unemployment rates. Application to the US setting was modeled differently, with non-drug costs estimated via an

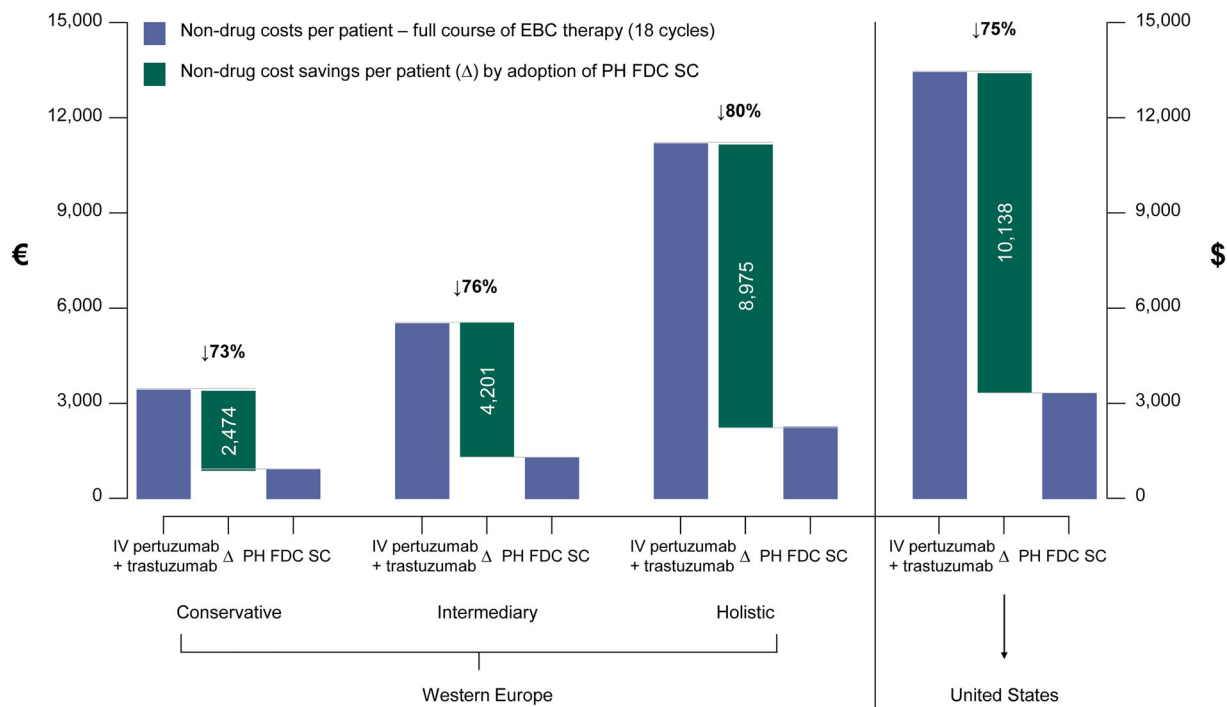
analysis of commercial claims data. As such, the Western Europe model was more reflective of value for healthcare providers and patients, while the US model was more relevant to payers.

The model-based, cost-minimization analysis aimed to estimate (roughly) potential cost differences between PH FDC SC and IV administration; and results showed that these differences were always in favor of PH FDC SC. Specifically, in Western Europe cost savings per patient with HER2-positive early breast cancer over a full course of therapy (18 cycles) were estimated in the range of €2474 (73% saving) to €8975 (80%) (Fig. 2). The scenario with lowest potential cost savings estimated non-drug costs at €3409 for IV pertuzumab and trastuzumab and €935 for PH FDC SC (Fig. 2). On the other hand, the scenario with most favorable projected outcomes estimated non-drug costs at €11,188 for IV pertuzumab and trastuzumab and €2213 for PH FDC SC (Fig. 2). In the US, from a payer's perspective, administration costs were estimated to be \$13,456 for IV pertuzumab and trastuzumab and \$3318 for PH FDC SC: a saving of \$10,138 (75%) (Fig. 2).

The authors found that non-drug cost savings were driven by a reduction in patient chair time (per the De Cock et al. definition [11]): up to 62% of total savings consisted of those derived from total chair time costs. Patients' productivity losses, on the other hand, had the least impact on cost savings and were estimated to explain up to 11% of non-drug cost differences. Furthermore, when cost elements were analyzed individually, the model for Western Europe estimated a saving of up to 85% on chair time costs, 76% on active HCPs' time costs, 65% on patients' productivity losses, and 69% on non-drug consumables costs.

The conservative scenario used irrefutable data as a source, i.e., SC injection time is shorter than IV infusion time. Other scenarios (such as the holistic scenario, adding CVAD implantation and cost data) included cost elements that may still have a significant impact on outcomes, but are harder to quantify as there are typically fewer data available.

It is to be noted that there is possible misalignment between reimbursement terms or fees in many countries and the potential healthcare providers' and patients' benefits



**Fig. 2** Non-drug cost savings per patient – full course of EBC therapy (18 cycles). *EBC* early breast cancer, *IV* intravenous, *PH FDC SC* fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection. Potential differences in observation times (beyond the monitoring during infusion/injection and subsequent immediate monitoring) were not taken into consideration, meaning that estimations were conservative overall. Reprinted with permission from Manevy F, Filkauskas

G, Levy P, Fredriksson J, and Sussell J. Potential non-drug cost differences associated with the use of the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection (PH FDC SC) in the treatment of HER2-positive early breast cancer patients in Western Europe and the United States. Poster 544; presented at the 2021 American Society of Clinical Oncology (ASCO) Virtual Congress, June 4–8, 2021

from PH FDC SC listed above, as a result of its shorter administration time versus IV infusions, for example, the cost to use a service in the EU versus how much is paid to conduct the service in the US—what a hospital is paid does not always equate to what is consumed in terms of resource, and vice-versa.

### HEALTHCARE PROFESSIONAL AND PATIENT EXPERIENCES OF PH FDC SC (FIG. 3)

#### Oncologist’s Perspective

Once PH FDC SC became available, we assessed 56 patients’ suitability to switch from IV

pertuzumab and trastuzumab dual blockade and discussed switching (and switching back if not satisfied) using teaching materials we developed alongside the manufacturer. We included patients in the early and metastatic settings receiving maintenance therapy and included patients receiving IV chemotherapy also. The switching rate was approximately 70–80%, regardless of age or therapy setting (e.g., neoadjuvant, adjuvant, or metastatic). Most patients appreciated the option of flexible appointment scheduling, including late in the afternoon after work, early in the morning before work, or even during their lunch break. Some patients were worried that they would not be able to switch back to IV infusions but we explained that it was an option. In the end, only

5% switched back to IV infusions for more-or-less anecdotal reasons and lots of patients asked for PH FDC SC around their vacations.

PH FDC SC is only administered into the thigh, with the injection site alternating at each administration between the left and right thigh. We have never had issues with privacy arising from injections into the thigh, as we have put measures in place (e.g., own room) from experience with SC trastuzumab.

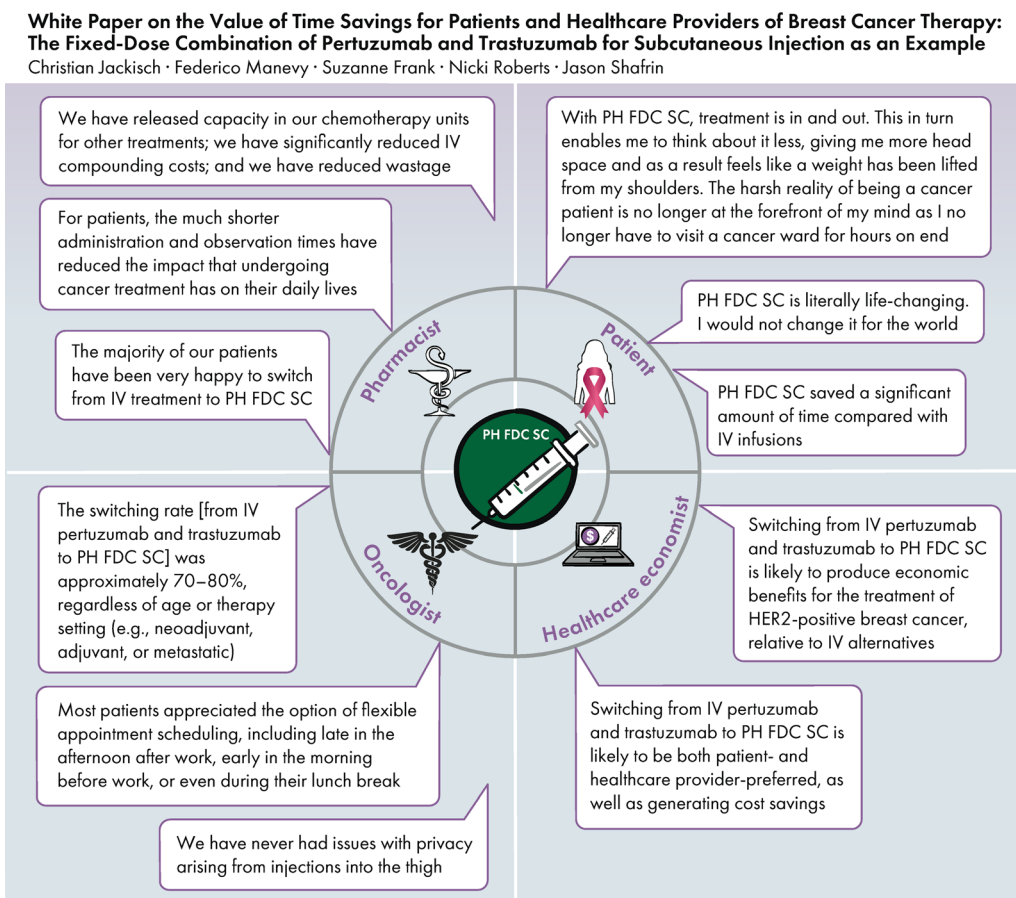
### Pharmacist's Perspective

The transition to PH FDC SC has had many benefits. First, for patients, the much shorter

administration and observation times have reduced the impact that undergoing cancer treatment has on their daily lives. The organizational benefits we have seen are that we have released capacity in our chemotherapy units for other treatments, we have significantly reduced IV compounding costs, and we have reduced wastage. The majority of our patients have been very happy to switch from IV treatment to PH FDC SC.

### Patient's Perspective

As someone who underwent mastectomy, chemotherapy, and radiotherapy as primary



The infographic represents the opinions of the authors. For a full list of declarations, including funding and author disclosure statements, please see the full text online. © The authors, CC-BY-NC [2021].

**Fig. 3** Healthcare professional and patient experience of PH FDC SC. *IV* intravenous, *PH FDC SC* fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection



treatment for breast cancer, followed by secondary treatment with chemotherapy and IV pertuzumab and trastuzumab before switching to PH FDC SC, in my experience the PH FDC SC saved a significant amount of time compared with IV infusions. The IV infusions could be a whole-day affair depending upon a number of factors, such as emergencies on the ward, delayed clinics, or other patients' needs and requirements, and whether the drugs were "ready-to-go" or not. Treatment with IV was rarely less than 3 h and was sometimes as much as 6.5 h. Cannulation was a difficult process due to the previous rounds of chemotherapy, which affected my veins. This often required a number of attempts before being successful and caused much discomfort. As delays could not be predicted, it was difficult to plan around treatment sessions (e.g., for childcare and work commitments). With PH FDC SC, treatment is in and out. This in turn enables me to think about it less, giving me more head space and as a result feels like a weight has been lifted from my shoulders. The harsh reality of being a cancer patient is no longer at the forefront of my mind as I no longer have to visit a cancer ward for hours on end. I now have a full day to plan as I wish, whether that involves family time or hobbies, rather than being in hospital all day.

PH FDC SC was also more convenient and efficient for the nurses, as they did not have to perform IV flushes or change infusion bags (which could therefore free up their time to see more patients).

One of the advantages that IV does have over PH FDC SC is the support network that is available on the ward (through being around the specialist nurses and the other patients); however, I have subsequently found that the advantages of PH FDC SC now far outweigh this. I have the same nurse each time I receive my treatment, who provides consistent support (as opposed to having differing nurses on the infusion ward). She has been able to help with my initial apprehension over switching. I also have the unfailing support of my family and friends, who have said that PH FDC SC is literally life-changing. I would not change it for the world.

## Healthcare Economist's Perspective

In terms of healthcare economics, switching from IV pertuzumab and trastuzumab to PH FDC SC is likely to be both patient- and healthcare provider-preferred, as well as generating cost savings. These savings are largely driven by shorter patient chair time, less active HCP time, and reduced non-drug consumable costs (e.g., isopropyl alcohol wipes, opaque infusion giving sets, NaCl). While in many cases the mode of administration may be more or less appealing to patients or healthcare providers, recent evidence shows that switching from IV pertuzumab and trastuzumab to PH FDC SC is likely to produce economic benefits for the treatment of HER2-positive breast cancer, relative to IV alternatives [22].

## CONCLUSION

Switching from IV pertuzumab and trastuzumab to PH FDC SC could reduce non-drug costs for healthcare providers treating HER2-positive breast cancer through time savings and other economic benefits. Furthermore, PH FDC SC could also save patient time given its shorter administration and observation time versus IV infusions, potentially resulting in reduced productivity loss. These benefits could be applied to other SC formulations, either currently available or in development.

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