Preference for the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection in patients with HER2-positive early breast cancer (PHranceSCa): a randomized, open-label phase II study

Article (Accepted Version)

Highlights

- PHranceSCa showed that most patients strongly preferred PH FDC SC over P + H IV
- PH FDC SC was generally well tolerated
- There were no new safety signals, even when switching
- PH FDC SC offers a quicker alternative to IV infusion

Preference for the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection in patients with HER2-positive early breast cancer (PHranceSCa): A randomized, open-label phase II study

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Abstract (247/250 words)

Aim

To assess patient preference for the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection (PH FDC SC) in patients with HER2-positive early breast cancer in PHranceSCa (NCT03674112).

Materials and methods

Patients completed neoadjuvant P + H + chemotherapy + surgery; were randomized 1:1 to three intravenous (IV) P + H cycles followed by three of PH FDC SC or vice versa (crossover); then chose SC or IV to continue up to 18 cycles (continuation). Assessments were via patient and healthcare professional (HCP) questionnaires.

Results

One hundred sixty patients were randomised (cutoff: February 24, 2020); 136 (85.0%, 95% CI: 78.5%–90.2%) preferred SC; 22 (13.8%) preferred IV; 2 (1.3%) had no preference. Main reasons for SC preference: reduced clinic time (n = 119); comfort during administration (n = 73). One hundred forty-one (88.1%) were very satisfied/satisfied with SC versus 108 (67.5%) with IV; 86.9% chose SC continuation. HCPs' perceptions of median patient treatment room time ranged from 33.0–50.0 min with SC and 130.0–300.0 min with IV.

Most adverse events (AEs) were grade 1/2 (no 4/5s); serious AE rates were low. AE rates before and after switching were similar (Cycles 1–3 IV → Cycles 4–6 SC: 77.5%→72.5%; Cycles 1–3 SC → Cycles 4–6 IV: 77.5%→63.8%).

Conclusion

Most patients strongly preferred PH FDC SC over P + H IV. PH FDC SC was generally well tolerated, with no new safety signals (even when switching), and offers a quicker alternative to IV infusion.

Keywords: Pertuzumab; Trastuzumab; Early breast cancer; Adjuvant; Subcutaneous; Fixed-dose; Patient-reported outcomes; Patient preference; Healthcare resource; Quality of life

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1. Introduction

Intravenous pertuzumab plus trastuzumab (P + H IV) with chemotherapy is standard-of-care for HER2-positive breast cancer (BC) both in the curative early BC (EBC) (as neoadjuvant–adjuvant and adjuvant treatment for patients at high risk of recurrence) and metastatic settings [1-4]. Despite their clinical benefits, they are infused sequentially over a long time, with observation, cannulation, line flushing, and waiting times that can total hours. This is burdensome for patients (especially those working throughout treatment and with collapsed veins) and healthcare systems. Repeated invasive IV treatments can be inconvenient and painful for patients [5, 6] and a burden on medical centers' time and resources [7].

A fixed-dose combination of P and H for subcutaneous injection (PH FDC SC) is FDA and EMA-approved for HER2-positive BC, and offers less invasive, faster administration than IV infusions. It has ~8-min loading and ~5-min maintenance administration times, and short observation times (minimum 30- and 15-min, respectively), giving patients convenience. Flexible care is an important consideration [8]; the FDA notes that PH FDC SC can be administered at home by a healthcare professional (HCP) [9]. PH FDC SC contains the same active ingredients as P + H IV and is noninferior in terms of P and H serum trough concentrations, with comparable pathologic complete response (pCR) rates and safety profiles (FeDeriCa study) [10].

While FeDeriCa focused on pharmacokinetics and clinical outcomes, the PHranceSCa study was designed to assess patients' preferences for PH FDC SC and P + H IV in HER2-positive EBC. We report the primary results.

2. Materials and methods

2.1 *Study design*

PHranceSCa (NCT03674112) is a randomized, open-label, international, multicenter, crossover, phase II study conducted at 39 sites in 16 countries. The design is shown in Fig. 1. Loading doses (P IV 840 mg; H IV 8 mg/kg; PH FDC SC 1200 mg P/600 mg H in 15 mL) were only required for patients who had ≥6 weeks since their last neoadjuvant dose of P + H IV at study entry, or had ≥6 weeks since their last study treatment during the study. Maintenance doses (P IV 420 mg; H IV 6 mg/kg; PH FDC SC 600 mg P/600 mg H in 10 mL) were used for subsequent administrations or dose delays <6 weeks.

2.2. *Patients*

Eligible patients were ≥18 years, had histologically confirmed HER2-positive (locally confirmed immunohistochemistry 3+ and/or in situ hybridization-positive) inflammatory, locally advanced, or early BC, had completed neoadjuvant P, H, and chemotherapy, and had subsequently undergone surgery for BC. Neoadjuvant chemotherapy regimen and number of neoadjuvant P + H cycles were at the physician's and patient's discretion. Patients had Eastern Cooperative Oncology Group performance status 0–1 and left ventricular ejection fraction (LVEF) ≥55% (by echocardiography or multiple-gated acquisition scan). Ineligibility criteria included previous systemic therapy (including chemotherapy, immunotherapy, HER2-targeted agents, endocrine therapy [selective estrogen receptor modulators, aromatase inhibitors], antitumor vaccines) for treatment/prevention of BC, except neoadjuvant P, H, and chemotherapy for current BC, serious cardiac illness/medical conditions, and impaired/inadequate organ/bone marrow function.

2.3. *Assessments*

The primary objective was to evaluate patient preference for PH FDC SC in the modified intent-to-treat (mITT) population, assessed as the proportion of patients who preferred PH FDC SC based on question 1 of the patient preference questionnaire (PPQ): “All things considered, which method of administration did you prefer?”

PPQ, therapy administration satisfaction questionnaire (TASQ), healthcare professional questionnaire (HCPQs), health-related quality of life, and safety assessments are described in Fig. 1.

2.4 *Statistical analysis*

The primary analysis was scheduled for when all patients had completed their last crossover treatment. The ITT population includes all randomized patients; the mITT population, all patients who received ≥1 dose of PH FDC SC and P + H IV during crossover and answered PPQ question 1.

The planned sample size (140) was based on an assumed 70% PH FDC SC preference. To achieve a distance of approximately ± 8% from the estimated proportion to 95% confidence interval (CI) limits, 126 were needed to evaluate preference. The final sample size was increased to ~140 patients to allow for 10% not providing an evaluable assessment.

Analyses were conducted using SAS Version 9.04 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. *Population*

Patient dispositions are shown in Fig. 2. Demographics and baseline characteristics were balanced (Table 1).

3.2. *Patient-reported outcomes*

136/160 patients (85.0%, 95% CI: 78.5–90.2) preferred PH FDC SC over P + H IV (22/160 [13.8%]) (Table 2).

Of those who preferred PH FDC SC, most (92.6%) indicated a “very/fairly strong” preference; the most common reasons were: “requires less time in the clinic” and “feels more comfortable during administration” (Table 2).

Of those who preferred P + H IV, 63.6% indicated a “very/fairly strong” preference; the most common reasons were: “feels more comfortable during administration” and “lower level of injection site pain” (Table 2).

Most patients (88.1%) indicated they were “(very) satisfied” with PH FDC SC (67.5% with P + H IV); most (71.3%) felt “not at all” restricted while receiving PH FDC SC (34.4% with P + H IV); 60.6% felt they “gained a lot of time” or “gained some time” with PH FDC SC (4.4% with P + H IV) (Table A.1).

Treatment had no impact on patient–HCP speaking time (PH FDC SC: 85%; P + H IV: 79%); most patients had more than enough time to talk to their HCP during treatment (PH FDC SC: 90%; P + H IV: 83%).

139/160 patients (86.9%) chose to continue with PH FDC SC after completing crossover (Arm A: 71/80 [88.8%]; Arm B: 68/80 [85.0%]).

Mean changes from baseline in global health status/health-related quality of life scale scores were minimal and comparable between arms throughout (Fig. A.1).

3.3. *Healthcare professional questionnaires*

957/960 HCPQs (99.7%) had ≥1 question answered in the drug preparation room during crossover (Table A.2). Median PH FDC SC preparation time was 5.0 min at all cycles (15.0–20.0 min for P + H IV). HCPs' perceptions of time indicated that for 140/160 patients (87.5%), HCPs agreed that PH FDC SC was quickest from preparation start to administration completion. Most HCPs "(strongly) agreed" that there would be less drug wastage due to PH FDC SC being ready to use, and that preparation procedures and associated time staff committed would be reduced if all IV infusions were switched to SC injections.

950/960 HCPQs (99.0%) had ≥1 question answered in the treatment room during crossover (Table A.3). Median patient time was 33.0–50.0 min with PH FDC SC and 130.0–300.0 min with P + H IV. Of this, median administration time was 7.0–8.0 min with PH FDC SC and 60.0–150.0 min with P + H IV.

3.4. *Treatment exposure*

During crossover, all patients received 3 cycles of each formulation. IV delays were reported for 9/160 patients (5.6%); SC delays, for 10/160 (6.3%). During continuation, 21 received IV infusions (median, 5 cycles initiated [range: 2–8]); 137 received SC injections (median, 5 cycles initiated [range: 1–9]). IV delays were reported for 2/21 (9.5%); SC delays, for 17/137 (12.4%). One patient originally chose and received one P + H IV dose during continuation, then chose PH FDC SC for the remaining cycles. Median exposure to neoadjuvant P + H IV was 4 cycles (range: 2–

8). At clinical cutoff, median exposure to adjuvant P + H (IV and SC) was 11 cycles (range: 6–15).

3.5. *Safety by crossover versus continuation period*

Most adverse events (AEs) were grade 1/2 (none 4/5), there were low rates of serious AEs, and no new safety signals were identified (Table 3). 70 patients per arm experienced AEs (87.5%). The only grade 3 event reported in >1 patient was device-related infection (one each during the IV and SC periods). The only serious AEs reported in >1 patient were the above-mentioned device-related infections, and decreased ejection fraction (two patients; considered treatment-related during crossover; grade 2).

Two patients discontinued treatment due to AEs: one due to the above-mentioned ejection fraction decrease with SC injection and one to disease relapse during continuation. This latter patient also experienced multiple AEs (nausea, ataxia, headache) related to this relapse that led to treatment withdrawal, all of which were grade 1/2 and considered unrelated to P + H IV; the grade 1 events (nausea, ataxia, headache) were ongoing at cutoff.

The most common AEs (in ≥5% of patients in any period) of any grade overall were radiation skin injury, injection site reaction, diarrhea, fatigue, arthralgia, hot flush, headache, myalgia, rash, and bone pain.

Anaphylaxis and hypersensitivity reactions (defined per the Sponsor's AE grouped terms) were reported for 4/160 patients (2.5%). All occurred with PH FDC SC, were non-serious injection-related reactions (no actual anaphylaxis reported) which were also considered administration-related reactions (ARRs; see below), were grade 1/2, and resolved.

ARRs were defined as “anaphylactic reaction (wide), anaphylaxis and hypersensitivity, and infusion-related reactions and hypersensitivity, occurring within 24 hours of the end of administration of HER2-targeted therapy, whether considered related or unrelated to study treatment by the investigator.” Onset timing of local injection site reactions was split between during/immediately after and within 24 hours of treatment. Onset timing of the single local infusion site reaction was within 24 hours of treatment. Systemic injection-related reactions related to SC administration were experienced by 3/160 patients (1.9%) during crossover and 2/137 (1.5%) during continuation. Onset timing of systemic injection-related reactions was within 24 hours of treatment. Onset timing of systemic infusion-related reactions was equally split between during/immediately after and within 24 hours of treatment. Other ARRs reported included headache, muscle spasms (both 2/160 patients [1.3%]), head discomfort, hypertension, and vomiting (1/160 patients each [0.6%]). All ARRs were grade 1/2 and resolved/resolving. None led to withdrawal/interruption of study treatment/were considered serious.

Cardiac AEs included ejection fraction decreases (7/160 patients [4.4%]), arrhythmia, tachycardia, and (cardiac ventricular) hypokinesia (1/160 patients each [0.6%]). No heart failures were reported. The ejection fraction decreases were reported during crossover: 3/160 patients (1.9%) during IV and 4/160 (2.5%) during SC administration. All were considered study treatment-related. Most were grade 2 and resolved (one was grade 3; another had not resolved). Treatment was interrupted for four patients (two each for PH FDC SC and P + H IV) and withdrawn for one (PH FDC SC).

The hypokinesia event was during IV crossover, considered non-serious, related to H, grade 2, resolved, and led to treatment interruption. The arrhythmia and

tachycardia events were each during SC administration in the crossover and continuation periods, respectively. Both were considered non-serious, grade 1, and unrelated to PH FDC SC. The arrhythmia had not resolved.

3.6. *Safety of switching between formulations*

AE rates before and after switching were similar (Cycles 1–3 IV → Cycles 4–6 SC: 78%→73%; Cycles 1–3 SC → Cycles 4–6 IV: 78%→64%) and did not reveal any new/clinically relevant safety concerns compared with the overall analysis (Table 3).

4. Discussion

The PHranceSCa primary analysis demonstrated that the vast majority of patients strongly preferred PH FDC SC over P + H IV; the main reasons being that patients spent less time in the clinic, and that they were more comfortable during administration.

Results were consistent with patients' treatment continuation choices: most chose to continue with SC injection after experiencing both methods and were (very) satisfied with PH FDC SC. Preferences were also clear despite PH FDC SC's relatively high injection volume and viscous formula, which may have concerned patients and less experienced HCPs [11]. However, providing that the person administering the injection has been trained to give it slowly, then patients, as reported here, should not have undue pain.

Results were consistent with similar studies (PrefHer [H SC versus H IV] [12, 13] and PrefMab [SC versus IV rituximab] [14]).

HCPQ data also supported PPQ data. There were notable time-savings for SC injection over IV infusion. HCPs indicated that SC injection led to time-savings for

preparation and administration, and reduced the overall time that patients spent in the treatment room and resource use. PrefHer showed that H SC injection reduces administration burden and chair time, and that it potentially optimises medical resource use [7].

There were no major changes during crossover in patients' health-related quality of life.

PH FDC SC was generally well tolerated. Incidences of AEs during crossover were identical between treatment arms, which indicates that treatment sequence had no effect on safety. Incidence during continuation was higher for IV versus SC; however, results should be interpreted with caution, as only 21 patients were evaluable for safety with IV infusion. There was a higher proportion of treatment-related AEs with PH FDC SC during crossover and continuation, the most common events being injection site reactions, as expected. This was also true for ARRs. Switching between IV and SC administration, or vice versa, was also well tolerated. Overall, safety results are supportive of those seen in FeDeriCa [10].

Our results provide important information not only for clinicians, but for patients. PH FDC SC use means that patients gain time for daily activities even with hospital visits every 3 weeks and that central venous access devices can be removed sooner, reducing the risk of morbidity. Another advantage is that patients do not need to go to an infusion room, necessarily – treatment can be administered by trained nurses outside of the hospital setting. There may be an added benefit that patients may feel more comfortable away from treatment rooms. In PrefHer, 60.4% of patients would hypothetically have preferred SC home administration [13]. This concept of flexible care is being investigated in an "oncology hospital-at-home program" in the USA, which reported fewer hospitalizations and emergency department visits, and reduced

costs versus standard processes [15]. Chemotherapy-at-home is a well-embedded UK practice. A UK study demonstrated that home care for patients with cancer, chronic conditions, and those needing end-of-life care may benefit patients with regards to better adherence, re-enablement, e.g. resuming or continuing daily activities, improved quality of life, improved patient activation, and financial savings [16]. The opportunity to move PH FDC SC administration by an HCP to the home was acknowledged by the FDA [9] and is particularly pertinent during the COVID-19 pandemic as a means of reducing the risk of infection associated with visiting hospitals (and the subsequent potential complications of COVID-19 infection in patients with cancer) [8]. An expanded access study (NCT04395508) is evaluating the safety of home-administered PH FDC SC by home health nurses. In addition to preparation and administration time-savings, PH FDC SC has a reduced observation time and may assist with avoiding having too many patients together in hospital at the same time. The clear preference expressed by most patients highlights the importance of HCP–patient dialogue, which was not impacted by PH FDC SC. Limitations include the small number of patients in the IV continuation period, and the lack of mature efficacy data. pCR data are available in FeDeriCa [10].

Conclusions

PHranceSCa showed that most patients strongly preferred PH FDC SC over P + H IV. PH FDC SC was generally well tolerated, with no new safety signals (even when switching from P + H IV to PH FDC SC, or vice-versa), and offers a quicker alternative to IV infusion.

Data sharing

Qualified researchers may request access to individual patient-level data through the clinical study data request platform: https://vivli.org/. Further details on Roche's criteria for eligible studies are available here: https://vivli.org/members/ourmembers/. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

Declaration of interest statement

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Table 1 Baseline patient demographic and tumor characteristics for the intent-to-treat population.

	Arm A	Arm B	
	P + H IV → PH FDC SC (n = 80)	PH FDC SC → P + H IV (n = 80)	All patients (N = 160)
Age, years			
Median	48.0	47.0	47.0
Range	26–74	22–80	22–80
Race			
American Indian or Alaska Native	5 (6.3)	3 (3.8)	8 (5.0)
Asian	8 (10.0)	4 (5.0)	12 (7.5)
Black or African American	2 (2.5)	2 (2.5)	4 (2.5)
White	62 (77.5)	67 (83.8)	129 (80.6)
Unknown	3 (3.8)	4 (5.0)	7 (4.4)
Baseline weight, kg			
Median	67.5	69.6	68.0
Range	46.4–99.0	47.5–119.0	46.4–119.0
ECOG performance status, n (%)			
0	70 (87.5)	70 (87.5)	140 (87.5)
1	10 (12.5)	10 (12.5)	20 (12.5)
Number of cycles of prior neoadjuvant P + H IV, n (%)			
<4	5 (6.3)	10 (12.5)	15 (9.4)

≥4	75 (93.8)	70 (87.5)	145 (90.6)
Prior neoadjuvant chemotherapy regimen (IxRS), n (%)			
Anthracyclines plus taxanes	55 (68.8)	53 (66.3)	108 (67.5)
Carboplatin plus taxanes	22 (27.5)	23 (28.8)	45 (28.1)
Taxanes only	3 (3.8)	4 (5.0)	7 (4.4)
Pathologic complete response to prior neoadjuvant treatment (IxRS), n (%)			
pCR	52 (65.0)	50 (62.5)	102 (63.8)
Residual disease	28 (35.0)	30 (37.5)	58 (36.3)
Hormone receptor status (IxRS), n (%)			
ER-positive and/or PgR-positive	53 (66.3)	51 (63.8)	104 (65.0)
ER-negative and PgR-negative	27 (33.8)	29 (36.3)	56 (35.0)
Histologic subtype, n (%)[a]			
Invasive carcinoma of no special type	44 (55.0)	50 (62.5)	94 (58.8)
Invasive lobular carcinoma	8 (10.0)	4 (5.0)	12 (7.5)
Invasive micropapillary carcinoma	1 (1.3)	1 (1.3)	2 (1.3)
Mucinous carcinoma	0	1 (1.3)	1 (0.6)
Apocrine carcinoma	0	1 (1.3)	1 (0.6)
Other	29 (36.3)	26 (32.5)	55 (34.4)
Histologic grade, n (%)			
G1	1 (1.3%)	2 (2.5)	3 (1.9)

G2	38 (47.5)	34 (42.5)	72 (45.0)
G3	30 (37.5)	37 (46.3)	67 (41.9)
No residual tumor	1 (1.3)	2 (2.5)	3 (1.9)
GX/unknown	10 (12.5)	5 (6.3)	15 (9.4)
Clinical stage at presentation, n (%)			
Stage II–IIIA	68 (85.0)	68 (85.0)	136 (85.0)
Stage IIIB–IIIC	12 (15.0)	12 (15.0)	24 (15.0)

All patients were female.

[a] Patients may have had more than one subtype; therefore, the same patient may have been counted in different categories.

ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; H, trastuzumab; IV, intravenous; IxRS, interactive voice/web response system; P, pertuzumab; PgR, progesterone receptor; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection.

Table 2 Patient preference in the modified intent-to-treat population.

	Arm A	Arm B	
	P + H IV → PH FDC SC (n = 80)	PH FDC SC → P + H IV (n = 80)	All patients (N = 160)
Preferred method of administration, n (%)			
Total number of respondents	80	80	160
SC	70 (87.5)	66 (82.5)	136 (85.0)
IV	10 (12.5)	12 (15.0)	22 (13.8)
No preference	0	2 (2.5)	2 (1.3)
How strong is this preference – SC?, n (%)			
Total number of respondents	70	66	136
Very strong	48 (68.6)	44 (66.7)	92 (67.6)
Fairly strong	17 (24.3)	17 (25.8)	34 (25.0)
Not very strong	5 (7.1)	5 (7.6)	10 (7.4)
Main reasons for the preference – SC, n (%)[a]			
Total number of responses	143	139	282
Feels less emotionally distressing	21 (14.7)	25 (18.0)	46 (16.3)
Requires less time in the clinic	60 (42.0)	59 (42.4)	119 (42.2)
Lower level of injection site pain	14 (9.8)	18 (12.9)	32 (11.3)
Feels more comfortable during administration	41 (28.7)	32 (23.0)	73 (25.9)

Other reason	7 (4.9)	5 (3.6)	12 (4.3)
How strong is this preference – IV?, n (%)			
Total number of respondents	10	12	22
Very strong	4 (40.0)	8 (66.7)	12 (54.5)
Fairly strong	1 (10.0)	1 (8.3)	2 (9.1)
Not very strong	5 (50.0)	3 (25.0)	8 (36.4)
Main reasons for the preference – IV, n (%)[a]			
Total number of responses	17	25	42
Feels less emotionally distressing	3 (17.6)	4 (16.0)	7 (16.7)
Requires less time in the clinic	1 (5.9)	1 (4.0)	2 (4.8)
Lower level of injection site pain	4 (23.5)	7 (28.0)	11 (26.2)
Feels more comfortable during administration	8 (47.1)	6 (24.0)	14 (33.3)
Other reason	1 (5.9)	7 (28.0)	8 (19.0)

Percentages are based on the total number of respondents/responses in the respective question and treatment sequence.

[a] Patients are counted in several categories.

H, trastuzumab; IV, intravenous; P, pertuzumab; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection.

Table 3 Adverse event profile during the crossover and continuation periods, and during switching between formulations (safety population; all patients who received ≥1 dose of any study drug).

Overall	P + H IV crossover (n = 160)	PH FDC SC crossover (n = 160)	P + H IV continuation (n = 21)	PH FDC SC continuation (n = 137)	All patients (N = 160)
Total number of patients with at least one AE, n (%)	113 (70.6)	120 (75.0)	13 (61.9)	70 (51.1)	144 (90.0)
Total number of AEs, n	308	339	41	213	901
Total number of patients with at least one, n (%)					
AE with fatal outcome	0	0	0	0	0
Related AE with fatal outcome	0	0	0	0	0
Grade 3 to 5 AE	6 (3.8)	4 (2.5)	2 (9.5)	4 (2.9)	13 (8.1)
Related grade 3 to 5 AE	1 (0.6)	1 (0.6)	0	0	2 (1.3)
Cardiac AEs (including LVEF events)	3 (1.9)	5 (3.1)	0	1 (0.7)	9 (5.6)
Serious AE	6 (3.8)	2 (1.3)	0	3 (2.2)	10 (6.3)
Suspected causal relationship to study medication					
Yes	30 (18.8)	58 (36.3)	2 (9.5)	27 (19.7)	79 (49.4)
Unknown	1 (0.6)	1 (0.6)	0	1 (0.7)	3 (1.9)
Local infusion site reaction	1 (0.6)	0	0	0	1 (0.6)
Systemic infusion-related reaction	6 (3.8)	0	0	0	6 (3.8)
Local injection site reaction	0	36 (22.5)	0	10 (7.3)	42 (26.3)
Systemic injection-related reaction	0	3 (1.9)	0	2 (1.5)	4 (2.5)

Switching	Arm A P + H IV → PH FDC SC		Arm B PH FDC SC → P + H IV		
	P + H IV (Cycles 1–3) (n = 80)	PH FDC SC (Cycles 4–6) (n = 80)	PH FDC SC (Cycles 1–3) (n = 80)	P + H IV (Cycles 4–6) (n = 80)	All patients (N = 160)
Total number of patients with at least one AE, n (%)	62 (77.5)	58 (72.5)	62 (77.5)	51 (63.8)	140 (87.5)
Total number of AEs, n	192	143	196	116	647
Five most common AEs (in ≥ 5% of patients), n (%)					
Radiation skin injury	17 (21.3)	7 (8.8)	10 (12.5)	10 (12.5)	43 (26.9)
Injection site reaction	0	12 (15.0)	24 (30.0)	0	36 (22.5)
Diarrhea	12 (15.0)	7 (8.8)	6 (7.5)	4 (5.0)	25 (15.6)
Fatigue	5 (6.3)	4 (5.0)	5 (6.3)	4 (5.0)	15 (9.4)
Hot flush	6 (7.5)	4 (5.0)	5 (6.3)	0	15 (9.4)

Percentages based on n/N in the column headings. Multiple occurrences of the same event in one individual were counted only once except for “Total number of AEs” row in which multiple occurrences of the same event were counted separately. Included are events with onset from first dose of any study treatment through 28 days after last dose of study treatment. When an event start date was partially or fully missing, and it was unclear to which treatment period the event should have been assigned, the event was assigned to all relevant treatment periods.

AE, adverse event; ARR, administration-related reaction; H, trastuzumab; IV, intravenous; LVEF, left ventricular ejection fraction; P, pertuzumab; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection.

FIGURE LEGENDS

Fig. 1. Study design.

[a] P IV loading dose if needed: 840 mg; maintenance: 420 mg q3w. H IV loading dose if needed: 8 mg/kg; maintenance: 6 mg/kg IV q3w.

[b] PH FDC SC loading dose if needed: P 1200 mg/H 600 mg in 15 mL; maintenance: P 600 mg/H 600 mg in 10 mL q3w.

[c] via European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30, at baseline, Cycle 3, Cycle 6, and the end of study treatment visits as well as at 18 months, 2 years, and 3 years from randomization).

[d] Via the incidence, nature, and severity of all investigator-reported adverse events, grade ≥3 adverse events, serious adverse events, and cardiac adverse events (including left ventricular ejection fraction events) with severity determined according to the National Cancer Institute's Common Terminology Criteria for Adverse Events v4.0; incidence of premature withdrawal from study treatment; targeted vital signs and physical findings; and targeted clinical laboratory test results.

Loading doses were only required for patients who had 6 or more weeks since their last neoadjuvant dose of P + H IV at study entry, or had 6 or more weeks since their last study treatment during the study. Maintenance doses were used for subsequent administrations or dose delays less than 6 weeks. Dose modifications were not allowed for HER2-targeted therapies, but administration could be delayed to assess or treat adverse events. Treatment was discontinued for disease recurrence, unacceptable toxicity, or patient withdrawal.

The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol was reviewed and approved by the

institutional review board or ethics committee at each study site. All patients provided written informed consent.

DXCX, Day X Cycle X; EBC, early breast cancer; ER, estrogen receptor; chemo, chemotherapy; H, trastuzumab; HCP, healthcare professional; HR, hormone receptor; IV, intravenous; NACT, neoadjuvant chemotherapy; P, pertuzumab; pCR, pathologic complete response; PgR, progesterone receptor; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection; PPQ, Patient Preference Questionnaire; q3w, every 3 week; R, randomization via a web-based response system; SC, subcutaneous; TASQ,Therapy Administration Satisfaction Questionnaire.

Fig. 2. Patient disposition.

[a] One patient in Arm A had not yet started continuation treatment.

[b] Seven patients in Arm A and nine in Arm B completed continuation treatment but had not yet started the follow-up period.

Data cutoff: February 24, 2020.

Reasons for exclusion between screening and randomisation:

Did not meet inclusion criteria (n = 11), met exclusion criteria (n = 10), patient decision (n = 1), and out of window (n = 1).

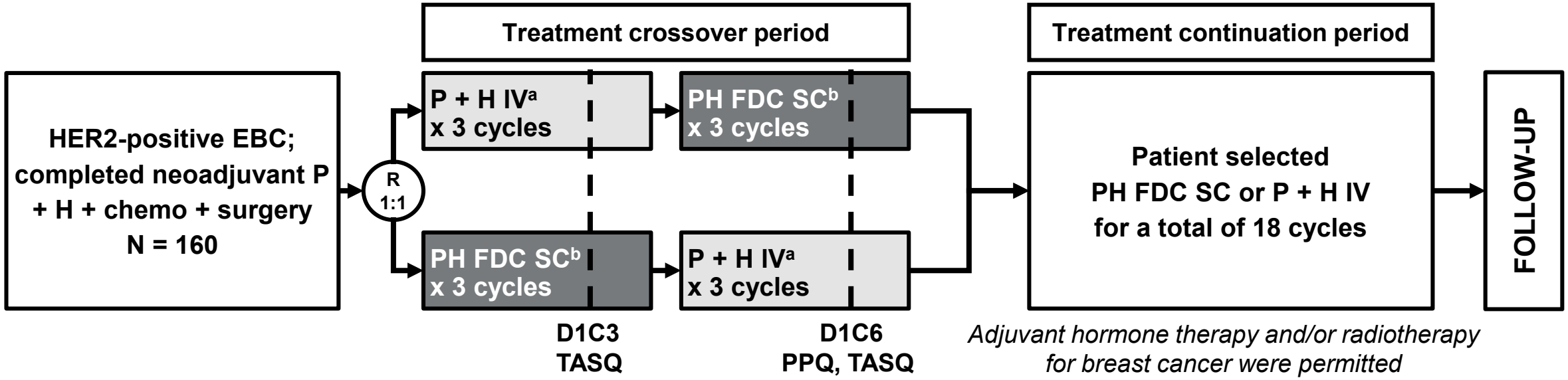
H, trastuzumab; IV, intravenous; P = pertuzumab; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection.

Fig. A.1. Change from baseline in mean global health status with 95% confidence intervals by treatment sequence in the patient-reported outcomes-evaluable population[a]

[a] 79 patients in Arm A and 80 in Arm B (one patient had no baseline and/or post-baseline assessment).

From Cycle 7 the formulation is based on the patient's choice for the continuation period, and the majority of patients chose the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection. Sequences are therefore no longer comparable at Cycle 15 or later.

DXCX, Day X Cycle X; H, trastuzumab; IV, intravenous; P, pertuzumab; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection.

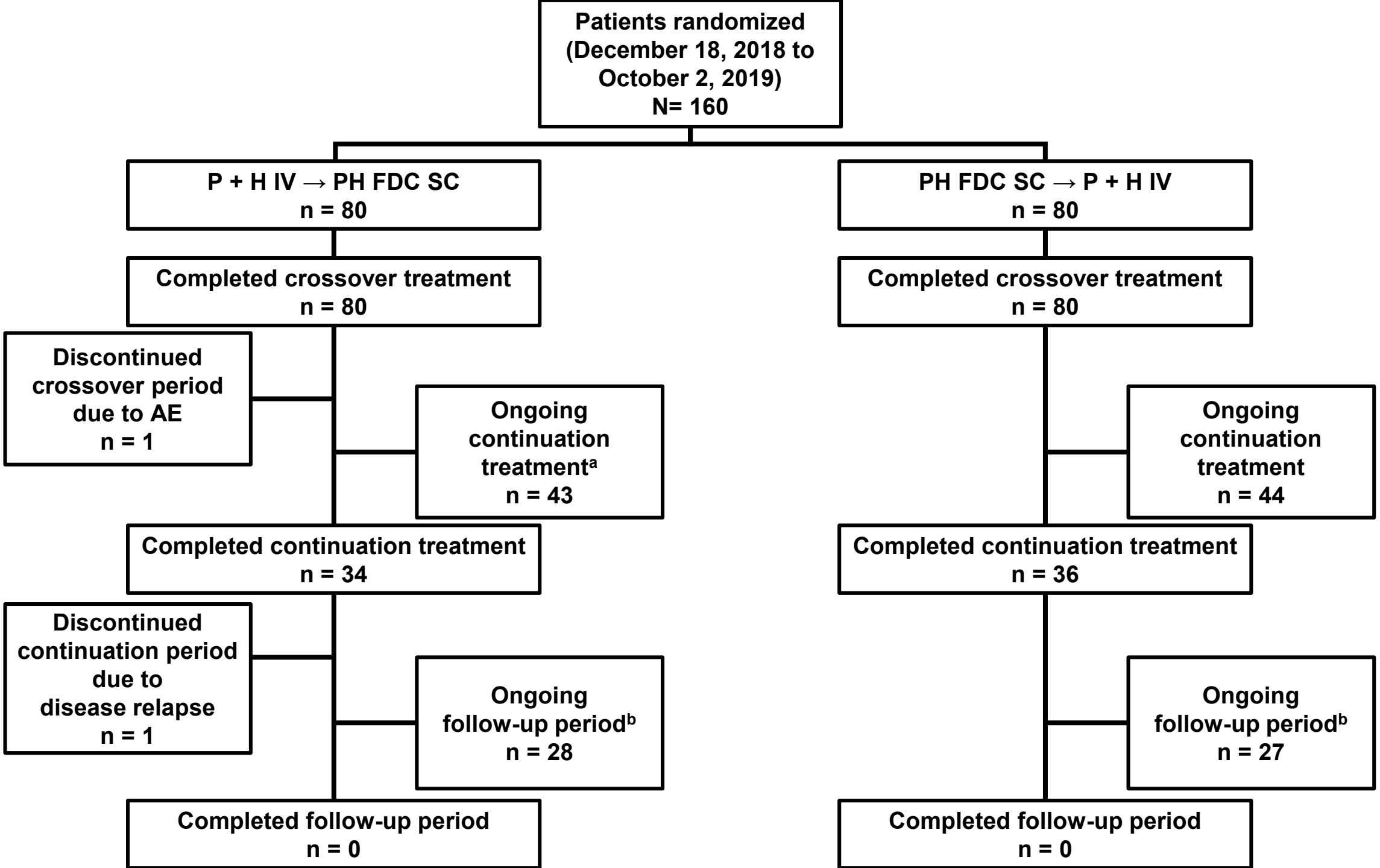


Stratification factors:

- NACT regimen (anthracyclines plus taxanes versus carboplatin plus taxanes versus taxanes only)
- pCR vs residual disease
- HR status (positive [ER-positive and/or PgR-positive] or negative [ER-negative and PgR-negative]

Primary objective: Patient preference for PH FDC SC

Key secondary objectives: Patient-assessed satisfaction with each route of administration; patients' choice of formulation for the continuation period; health-related quality of life,[c] HCP perception on time/resource use at each cycle during the treatment crossover period, safety and tolerability during the crossover period and the entire adjuvant treatment period i.e. including continuation (including safety of switching from SC to IV formulations and vice versa),[d] efficacy (to be reported once data are mature)


Patients randomized
(December 18, 2018 to
October 2, 2019)
N= 160
P + H IV → PH FDC SC
n = 80
PH FDC SC → P + H IV
n = 80
Completed crossover treatment
n = 80
Completed crossover treatment
n = 80
Discontinued
crossover period
due to AE
n = 1
Ongoing
continuation
treatment[a]
n = 43
Ongoing
continuation
treatment
n = 44
Completed continuation treatment
n = 34
Completed continuation treatment
n = 36
Discontinued
continuation period
due to
disease relapse
n = 1
Ongoing
follow-up period[b]
n = 28
Ongoing
follow-up period[b]
n = 27
Completed follow-up period
n = 0
Completed follow-up period
n = 0

The following investigators participated in the PHranceSCa study:

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Table A.1 Therapy Administration Satisfaction Questionnaire responses in the modified intent-to-treat population.

n (%)	Arm A P + H IV → PH FDC SC (n = 80)	Arm B PH FDC SC → P + H IV (n = 80)	All Patients (N = 160)
Patient satisfaction, question 1			
TASQ-IV			
How satisfied or dissatisfied were you with the IV infusion?			
Very satisfied	23 (28.8)	18 (22.5)	41 (25.6)
Satisfied	37 (46.3)	30 (37.5)	67 (41.9)
Neither satisfied nor dissatisfied	17 (21.3)	24 (30.0)	41 (25.6)
Dissatisfied	2 (2.5)	7 (8.8)	9 (5.6)
Very dissatisfied	1 (1.3)	1 (1.3)	2 (1.3)
TASQ-SC			
How satisfied or dissatisfied were you with the SC injection?			
Very satisfied	41 (51.3)	51 (63.8)	92 (57.5)
Satisfied	29 (36.3)	20 (25.0)	49 (30.6)
Neither satisfied nor dissatisfied	5 (6.3)	2 (2.5)	7 (4.4)
Dissatisfied	1 (1.3)	2 (2.5)	3 (1.9)
Very dissatisfied	4 (5.0)	3 (3.8)	7 (4.4)
Patient did not answer question	0	2 (2.5)	2 (1.3)
Psychological impact domain			
TASQ-IV			
When receiving the IV infusion, do you feel restricted?			

Not at all	26 (32.5)	29 (36.3)	55 (34.4)
A little bit	32 (40.0)	17 (21.3)	49 (30.6)
Somewhat	12 (15.0)	17 (21.3)	29 (18.1)
Quite a bit	9 (11.3)	10 (12.5)	19 (11.9)
Very much	1 (1.3)	7 (8.8)	8 (5.0)
TASQ-SC			
When receiving the SC injection, do you feel restricted?			
Not at all	57 (71.3)	57 (71.3)	114 (71.3)
A little bit	20 (25.0)	15 (18.8)	35 (21.9)
Somewhat	2 (2.5)	1 (1.3)	3 (1.9)
Quite a bit	1 (1.3)	4 (5.0)	5 (3.1)
Patient did not answer question	0	3 (3.8)	3 (1.9)
Impact on activities of daily living			
TASQ-IV			
Does setting up the IV infusion mean you lose or gain time for other things?			
Lost a lot of time	12 (15.0)	22 (27.5)	34 (21.3)
Lost some time	35 (43.8)	28 (35.0)	63 (39.4)
Neither lost nor gained time	30 (37.5)	26 (32.5)	56 (35.0)
Gained some time	1 (1.3)	2 (2.5)	3 (1.9)
Gained a lot of time	2 (2.5)	2 (2.5)	4 (2.5)
TASQ-SC			
Does setting up the SC injection mean you lose or gain time for other things?			
Lost a lot of time	0	1 (1.3)	1 (0.6)
Lost some time	8 (10.0)	5 (6.3)	13 (8.1)
Neither lost nor gained time	22 (27.5)	23 (28.8)	45 (28.1)

Gained some time	23 (28.8)	19 (23.8)	42 (26.3)
Gained a lot of time	26 (32.5)	29 (36.3)	55 (34.4)
Patient did not answer question	1 (1.3)	3 (3.8)	4 (2.5)

H, trastuzumab; IV, intravenous; P, pertuzumab; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection; TASQ, Therapy Administration Satisfaction Questionnaire.

Table A.2 Healthcare Professional Questionnaire responses in the drug preparation room.[a]

	Arm A	Arm B	
	P + H IV → PH FDC SC (n = 80)	PH FDC SC → P + H IV (n = 80)	All patients (N = 160)
How long (in minutes) did it take to prepare the treatment for use, median (range)?			
Cycle 1	IV; n = 80	SC; n = 79	
	20.0 (3–60)	5.0 (1–50)	
Cycle 2	IV; n = 79	SC; n = 80	
	20.0 (3–60)	5.0 (1–30)	
Cycle 3	IV; n = 80	SC; n = 80	
	17.5 (3–90)	5.0 (1–40)	
Cycle 4	SC; n = 80	IV; n = 80	
	5.0 (1–30)	15.0 (3–49)	
Cycle 5	SC; n = 80	IV; n = 79	
	5.0 (1–35)	15.0 (3–50)	
Cycle 6	SC; n = 80	IV; n = 80	
	5.0 (1–40)	15.0 (3–50)	
Looking back over the pertuzumab–trastuzumab drug preparation sessions, please indicate which administration method was quickest from start to end of preparation to finish of administration (excluding observation period), n (%)			
PH FDC SC	74 (92.5)	66 (82.5)	140 (87.5)
P + H IV	0	1 (1.3)	1 (0.6)
No difference	1 (1.3)	1 (1.3)	2 (1.3)

Missing	5 (6.3)	12 (15.0)	17 (10.6)
If all P + H IV infusions are switched to PH FDC SC injections, please indicate how strongly you agree or disagree with each of the following, n (%)			
Due to ready-to-use PH FDC SC formulations, there will be less drug wastage			
Strongly disagree	1 (1.3)	1 (1.3)	2 (1.3)
Disagree	1 (1.3)	2 (2.5)	3 (1.9)
Neutral	9 (11.3)	5 (6.3)	14 (8.8)
Agree	17 (21.3)	18 (22.5)	35 (21.9)
Strongly agree	47 (58.8)	41 (51.3)	88 (55.0)
Not applicable	1 (1.3)	2 (2.5)	3 (1.9)
Missing	4 (5.0)	11 (13.8)	15 (9.4)
Preparation procedures and associated staff time commitment with be reduced			
Strongly disagree	0	1 (1.3)	1 (0.6)
Neutral	7 (8.8)	4 (5.0)	11 (6.9)
Agree	24 (30.0)	26 (32.5)	50 (31.3)
Strongly agree	42 (52.5)	36 (45.0)	78 (48.8)
Not applicable	3 (3.8)	2 (2.5)	5 (3.1)
Missing	4 (5.0)	11 (13.8)	15 (9.4)

[a] The place where P + H IV reconstitution or PH FDC SC is prepared before the actual drug administration takes place. Thus, “drug preparation area” can refer to the hospital pharmacy or to a special aseptic drug preparation area within the day oncology unit.

H trastuzumab; IV, intravenous; P, pertuzumab; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection.

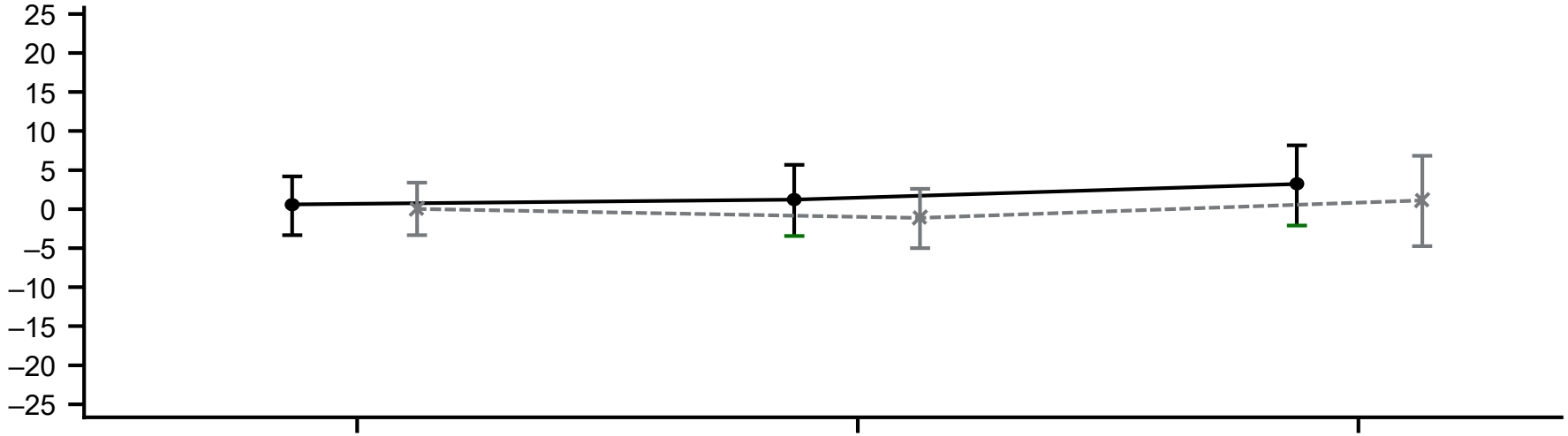
Table A.3 Healthcare Professional Questionnaire responses in the treatment room.

	Arm A	Arm B
	P + H IV → PH FDC SC (n = 80)	PH FDC SC → P + H IV (n = 80)
How long (in minutes) did it take to administer the treatment, median (range)?		
Cycle 1	IV; n = 79	SC; n = 79
	150.0 (60–396)	8.0 (2–17)
Cycle 2	IV; n = 77	SC; n = 80
	90.0 (8–260)	8.0 (5–20)
Cycle 3	IV; n = 79	SC; n = 80
	70.0 (30–420)	7.5 (4–16)
Cycle 4	SC; n = 80	IV; n = 77
	8.0 (4–12)	60.0 (30–120)
Cycle 5	SC; n = 79	IV; n = 77
	8.0 (3–14)	83.0 (30–200)
Cycle 6	SC; n = 79	SC; n = 80
	7.0 (3–11)	60.0 (5–275)
How long (in minutes) was the patient in the treatment room for in total, median (range)?		
Cycle 1	IV; n = 79	SC; n = 79
	300.0 (90–450)	50.0 (8–240)
Cycle 2	IV; n = 77	SC; n = 78
	153.0 (30–342)	40.0 (8–225)

Cycle 3	IV; n = 79	SC; n = 79
	150.0 (105–330)	36.0 (5–327)
Cycle 4	SC; n = 78	SC; n = 77
	45.0 (1–185)	150.0 (80–480)
Cycle 5	SC; n = 79	SC; n = 77
	33.0 (8–135)	150.0 (95–343)
Cycle 6	SC; n = 79	SC; n = 80
	35.0 (10–150)	130.0 (45–330)

Data are median (range).

H, trastuzumab; IV, intravenous; P, pertuzumab; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection.



	Number of patients			
———	Arm A: P + H IV → PH FDC SC (n = 79)	77	76	31
- - - - -	Arm B: PH FDC SC → P + H IV (n = 80)	80	79	33