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Original Research

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

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☆☆ Key patient preference data from the current primary analysis are included in the USPI, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761170s000lbl.pdf.

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Quality of life

**Abstract** ***Aim:*** The aim of the study was 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 who completed neoadjuvant P + H + chemotherapy + surgery were randomised 1:1 to three intravenous (IV) P + H cycles followed by three cycles of PH FDC SC or vice versa (crossover) and then chose subcutaneous (SC) injection or IV infusion to continue up to 18 cycles (continuation). Assessments were via patient and healthcare professional (HCP) questionnaires.
***Results:*** One hundred and sixty patients were randomised (cut-off: 24 February 2020); 136 (85.0%, 95% confidence interval: 78.5–90.2%) preferred SC; 22 (13.8%) preferred IV; 2 (1.3%) had no preference. The main reasons for SC preference were reduced clinic time (n = 119) and comfort during administration (n = 73). One hundred and forty-one patients (88.1%) were very satisfied/satisfied with SC injection versus 108 (67.5%) with IV infusion; 86.9% chose PH FDC SC continuation. HCP 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.


## 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 centres' time and resources [7].

A fixed-dose combination of P and H for subcutaneous injection (PH FDC SC) is US Food and Drug Administration (FDA)- and European Medicines Agency (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 non-inferior in terms of P and H serum trough concentrations, with comparable pathological 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 randomised, open-label, international, multicentre, 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 old, had histologically confirmed HER2-positive (locally confirmed immunohistochemistry 3+ and/or in situ hybridisation-positive) inflammatory, locally advanced or EBC, had completed neoadjuvant P, H and chemotherapy and had subsequently undergone surgery for BC. The neoadjuvant chemotherapy regimen and number of neoadjuvant P + H cycles were at the physician's and patient's discretion. Patients had an Eastern Cooperative Oncology Group performance status of 0–1 and left ventricular ejection fraction ≥55% (by echocardiography or multiple-gated acquisition scan). Ineligibility criteria included previous systemic therapy (including chemotherapy, immunotherapy, HER2-targeted agents, endocrine therapy [selective oestrogen receptor modulators, aromatase inhibitors] and anti-tumour 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 intention-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?"

The PPQ, Therapy Administration Satisfaction Questionnaire, HCP Questionnaire (HCPQ), health-related quality of life and safety assessments are described in Fig. 1.

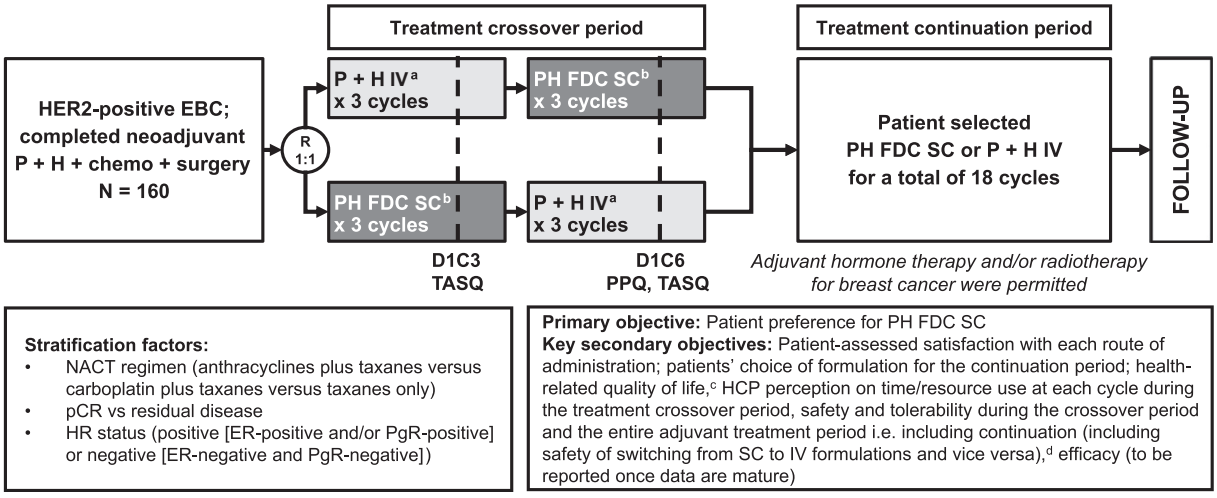


Fig. 1. Study design. Loading doses were only required for patients who had 6 or more weeks since their last neoadjuvant dose of P + H IV at study entry or had 6 or more weeks since their last study treatment during the study. Maintenance doses were used for subsequent administrations or dose delays 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, oestrogen receptor; chemo, chemotherapy; H, trastuzumab; HCP, healthcare professional; HR, hormone receptor; IV, intravenous; NACT, neoadjuvant chemotherapy; P, pertuzumab; pCR, pathological 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 weeks; R, randomisation via a web-based response system; SC, subcutaneous; TASQ, Therapy Administration Satisfaction Questionnaire.
[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 randomisation. [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 version 4.0; incidence of premature withdrawal from study treatment; targeted vital signs and physical findings and targeted clinical laboratory test results.

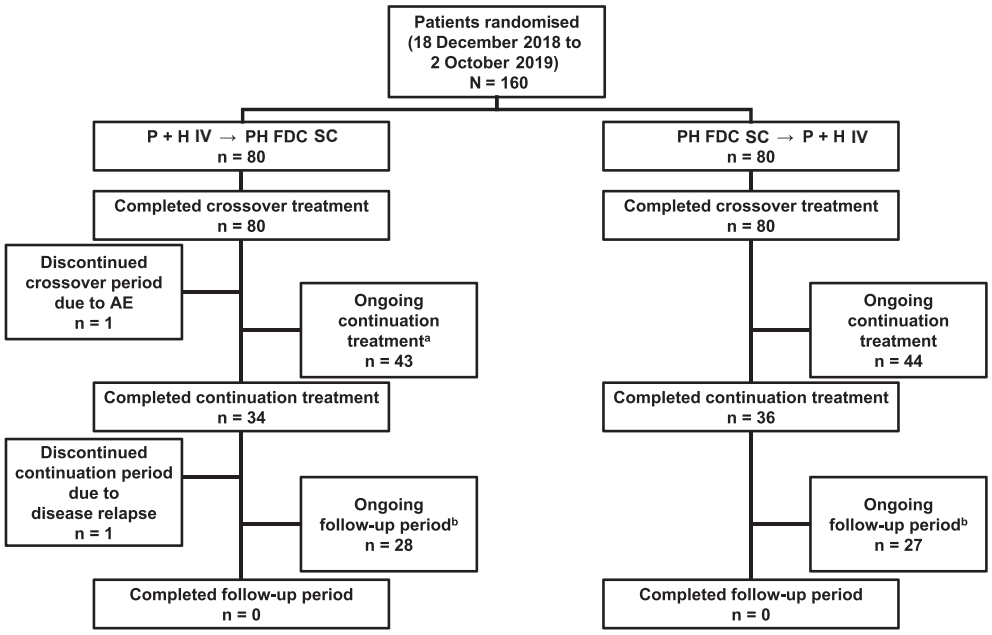


Fig. 2. Patient disposition. Reasons for exclusion between screening and randomisation: Did not meet inclusion criteria (n = 11), met exclusion criteria (n = 10), patient decision (n = 1) and out of window (n = 1). H, trastuzumab; IV, intravenous; P = pertuzumab; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection.
[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 cut-off: 24 February 2020.

### 2.4. Statistical analysis

The primary analysis was scheduled for when all patients had completed their last crossover treatment. The intention-to-treat (ITT) population includes all randomised patients. The mITT population includes 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

One hundred and thirty-six of 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 A1).

Treatment had no impact on patient–HCP speaking time (PH FDC SC: 85.0%; P + H IV: 79.4%); most patients had more than enough time to talk to their HCP during treatment (PH FDC SC: 90.0%; P + H IV: 82.5%).

One hundred and thirty-nine of 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. A1).

### 3.3. HCPQs

Nine hundred and fifty-seven of 960 HCPQs (99.7%) had ≥1 question answered in the drug preparation room during crossover (Table A2). 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 because of 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.

Nine hundred and fifty of 960 HCPQs (99.0%) had ≥1 question answered in the treatment room during crossover (Table A3). The 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, the 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 were reported for 10/160 patients (6.3%).

Table 1
Baseline patient demographic and tumour characteristics for the intention-to-treat population.

| | Arm A | Arm B | All patients (N = 160) |
|---|---|---|---|
| | P + H IV → PH FDC SC (n = 80) | PH FDC SC → P + H IV (n = 80) | |
| 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) |
| Pathological 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) |
| Histological 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) |
| Histological 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 tumour | 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 women. ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; H, trastuzumab; IV, intravenous; IxRS, interactive voice/web response system; P, pertuzumab; pCR, pathological complete response; PgR, progesterone receptor; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection.

[a] Patients may have had >1 subtype; therefore, the same patient may have been counted in different categories.

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

| | Arm A | Arm B | All patients (N = 160) |
|---|---|---|---|
| | P + H IV → PH FDC SC (n = 80) | PH FDC SC → P + H IV (n = 80) | |
| 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. H, trastuzumab; IV, intravenous; P, pertuzumab; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection.
[a] Patients are counted in several categories.

During continuation, 21 patients received IV infusions (median, 5 cycles initiated [range: 2–8]); 137 patients received SC injections (median, 5 cycles initiated [range: 1–9]). IV delays were reported for 2/21 patients (9.5%); SC delays were reported for 17/137 patients (12.4%). One patient originally chose and received one P + H IV dose during continuation and then chose PH FDC SC for the remaining cycles. The median exposure to neoadjuvant P + H IV was 4 cycles (range: 2–8). At clinical cut-off, the 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). Seventy 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 aforementioned device-related infections and decreased ejection fraction (two patients; considered treatment related during crossover; grade 2).

Two patients discontinued treatment because of AEs: one because of the aforementioned ejection fraction decrease with SC injection and one because of 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 cut-off.

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

Anaphylaxis and hypersensitivity reactions (defined as per the Sponsor's AE grouped terms) were reported for 4/160 patients (2.5%). All occurred with

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 ≥1 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 ≥1, n (%): | | | | | |
| AE with fatal outcome | 0 | 0 | 0 | 0 | 0 |
| Related AE with fatal outcome | 0 | 0 | 0 | 0 | 0 |
| Grade 3–5 AE | 6 (3.8) | 4 (2.5) | 2 (9.5) | 4 (2.9) | 13 (8.1) |
| Related grade 3–5 AE | 1 (0.6) | 1 (0.6) | 0 | 0 | 2 (1.3) |
| Cardiac AE (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 | | Arm B | | All patients (N = 160) |
| | P + H IV → PH FDC SC | | 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) | |
| Total number of patients with ≥ 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) |
| Diarrhoea | 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 are 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 the first dose of any study treatment through 28 days after the 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.

PH FDC SC, were non-serious injection-related reactions (no actual anaphylaxis reported) which were also considered administration-related reactions (ARRs; please see the following paragraph), 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 h 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 h of treatment. Onset timing of the single local infusion site reaction was within 24 h of treatment. Systemic injection-related reactions related to SC administration were experienced by 3/160 patients (1.9%) during crossover and by 2/137 patients (1.5%) during continuation. Onset timing of systemic injection-related reactions was within 24 h of treatment. Onset timing of systemic infusion-related reactions was equally split between during/immediately after and within 24 h 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 in 3/160 patients (1.9%) during IV administration and 4/160 patients (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 also 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 US, which reported fewer hospitalisations 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, patients with chronic conditions and those needing end-of-life care may benefit patients with regard to better adherence, reenablement, for example, 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 the 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].

## 5. 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.

## Author contributions

J.O.'S.: Writing – review & editing; Investigation. S.S.: Writing – review & editing; Investigation. J.C.: Writing – review & editing; Investigation; Validation; Visualisation. L.F.: Writing – review & editing; Conceptualisation. P.A.: Writing – review & editing; Resources; Investigation. C.P.: Writing – review & editing; Investigation; Validation; Visualisation. A.C.: Writing – review & editing; Investigation. S.W.: Writing – review & editing; Investigation; Data review. L.R.: Writing – review & editing; Investigation; Validation; Visualisation. M.B.: Writing – review & editing; Investigation; Validation. D.K.: Writing – review & editing; Formal analysis; Methodology. D.M.: Writing – review & editing; Formal analysis; Methodology. A.A.: Writing – review & editing; Formal analysis; Methodology. P.T.: Writing – review & editing; Data review & interpretation. J.F.: Writing – review & editing; Formal analysis; Validation; Visualisation. Z.M.: Writing – review & editing; Conceptualisation. L.S.: Writing – review & editing; Investigation, Validation; Visualisation.

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## Conflict of interest statement

J.O.'S. reports consultancy/advisory roles for AbbVie, Agendia, Amgen, AstraZeneca, BMS, Celgene, Eisai, Genentech, Inc., Immunomedics, Ipsen, Lilly, Merck, Novartis, Odonate, Pfizer, Puma, Prime Oncology, F. Hoffmann-La Roche Ltd, Seattle Genetics and Daiichi Sankyo. S.S. reports funding for travelling, congresses, lectures and advisory boards from F. Hoffmann-La Roche Ltd, Novartis, Pfizer, Tesaro, AstraZeneca, MSD, Pierre Fabre and Eisai. J.C. reports speaker honoraria from GSK, AstraZeneca, F. Hoffmann-La Roche Ltd, Novartis, PharmaMar, Eisai, Lilly, Celgene, Astellas, Amgen and Pfizer and consultant/advisory roles for GSK, AstraZeneca, F. Hoffmann-La Roche Ltd, Novartis, PharmaMar, Eisai, Lilly, Celgene, Astellas, Amgen and Pfizer. L.F. reports honoraria from Pfizer, AstraZeneca, BMS, Lilly, Novartis, Exact Sciences and Veracyte. P.A. reports funding for the ESMO Breast Cancer Congress 2019. C.P. reports public speaking for AstraZeneca, Grunenthal and Novartis and writing engagements from AstraZeneca. A.C. reports speaker honoraria from Novartis, Pfizer, AstraZeneca and F. Hoffmann-La Roche Ltd. S.W. reports payment for an advisory board from Seattle Genetics. L.R. reports payments for speaking and advisory boards from Roche Pharmaceuticals, Merck Serono, MSD, BMS, AstraZeneca and Pfizer and for personal medical education and participation in congresses from BMS, Roche Pharmaceuticals, Merck Serono, Pfizer, Amgen and Pierre Fabre. M.B. reports payments for advisory boards, speaking at industry symposiums and consulting roles from F. Hoffmann-La Roche Ltd, MSD, BMS, AstraZeneca and Novartis. D.K. is an employee of, and owns stocks in, F. Hoffmann-La Roche Ltd. D.M. is an employee of F. Hoffmann-La Roche Ltd. A.A. is an employee of Roche Products Limited and owns stocks in F. Hoffmann-La Roche Ltd. P.T. is an employee of, and

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## Appendix A. Supplementary data

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