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Clinical Trial

Safety profile of subcutaneous trastuzumab for the treatment of patients with HER2-positive early or locally advanced breast cancer: primary analysis of the SCHEARLY study



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KEYWORDS

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breast cancer;
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Abstract Background: Subcutaneous trastuzumab (H SC) is a valuable alternative to the intravenous formulation. This study assessed H SC safety and tolerability in human epidermal growth factor receptor 2 (HER2)+ early/locally advanced breast cancer (EBC/LABC).

Methods: SCHEARLY is a prospective, two-cohort, non-randomised, multicentre Italian trial included in the umbrella study UmbHER1, planning a 1-year treatment with H SC 600 mg in

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Safety;
Subcutaneous
trastuzumab

HER2+ EBC/LABC. Patients were sequentially assigned to cohort A (N = 121) and B (N = 119) to receive H SC via a handheld syringe and a single-use injection device, respectively. Adjuvant or neoadjuvant treatment included anthracycline-containing regimens followed by H SC plus taxanes and then alone for 18 cycles totally.

Results: Two hundred forty patients were enrolled (adjuvant therapy: 81.7%; neoadjuvant therapy: 18.3%), and 201 completed the treatment (early discontinuation was mainly due to intercurrent adverse events [AEs], 7.5%). Overall, the two cohorts displayed similar safety profiles. From H SC start, the rate of treatment-related AEs in the safety population (N = 228) was 3.9% for grade ≥ 3 AEs; 0.9% for serious AEs (one pleuropericarditis and one anaphylactic shock, both resolved) and 14.5% for cardiac AEs, the most common being the decreased left ventricular ejection fraction (7.9%; mean reduction from the screening to the follow-up visit was 2.9%). No cases of congestive heart failure occurred. The rate of systemic administration-related reactions and local injection site reactions was 68.0% and 21.9%, respectively, mostly of grade 1–2.

Conclusions: H SC 600 mg confirmed to be a safe and tolerable option as adjuvant/neoadjuvant therapy in patients with HER2+ EBC and LABC.

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1. Introduction

The humanised monoclonal antibody trastuzumab is the current standard of care for the treatment of patients with HER2-positive breast cancer (BC) [1–3]. Indeed, in combination with chemotherapy (CT), it significantly improved disease-free survival and overall survival compared with CT alone [4]. The intravenous (IV) trastuzumab formulation was approved in HER2-positive BC in 1998 [5]. As an alternative, a fixed-dose subcutaneous (SC) formulation containing the recombinant humanised hyaluronidase [6] was developed (F. Hoffmann-La Roche Ltd). Humanised hyaluronidase, that temporarily degrades interstitial hyaluronan in the subcutaneous space, enables the administration of large drug volumes subcutaneously and favours trastuzumab delivery to the circulation, significantly shortening the administration time (5 min for SC vs. 30–90 min for IV). A conventional handheld syringe (vial) and a single-use injection device (SID) were developed [7], both used in the present study.

The SC formulation was approved after the pivotal phase III HannaH study that demonstrated similar safety and efficacy profiles of Herceptin® (H, F. Hoffmann-La Roche Ltd, Basel, Switzerland) SC and H IV in patients with HER2-positive early BC (EBC) [8]. In this setting, H SC displayed a low rate of clinically relevant adverse events (AEs), especially of treatment-related AEs such as administration site reactions [9–11]. Moreover, in the PrefHer study, H SC was preferred over H IV by 98% of patients, regardless of the vial or SID [9,11].

H therapy has been associated with cardiotoxicity, represented by left ventricular ejection fraction (LVEF) reduction with or without clinical signs and symptoms

of heart failure (HF) [12,13], that was, however, generally reversible [13].

The primary objective of the SCHEARLY study was to extend the knowledge on H SC (vial or SID) safety to a broader range of patients with HER2-positive BC, with a specific focus on administration-related side-effects and cardiotoxicity [12,13].

2. Patients and methods

2.1. Study design

SCHEARLY is a prospective, two-cohort, non-randomised, multicentre, open-label Italian trial, participating in the global umbrella study UmbHER1 [14], including patients with HER2-positive EBC/locally advanced breast cancer (LABC) eligible for adjuvant or neoadjuvant anti-HER2 therapy.

As illustrated in Fig. 1, patients were sequentially assigned to cohort A and treated with H SC 600 mg/5 mL via a conventional syringe (vial) or to cohort B and received H SC 600 mg/5 mL through a self-administered SID. In each cohort, patients were also allocated to adjuvant (group 1) or neoadjuvant therapy (group 2), based on the investigator's choice.

All patients received sequential conventional CT regimens including four cycles of anthracycline-based CT (epirubicin 90 mg/m² or doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² $\pm$ fluorouracil 600 mg/m² every 3 weeks) followed by the taxane-based regimen (weekly paclitaxel 80 mg/m² or 75/100 mg/m² docetaxel every 3 weeks) concomitantly with H SC every 3 weeks for 12 weeks (four cycles totally). At the end of CT, patients with triple-positive disease could receive hormone therapy as per the clinical practice. The study drug

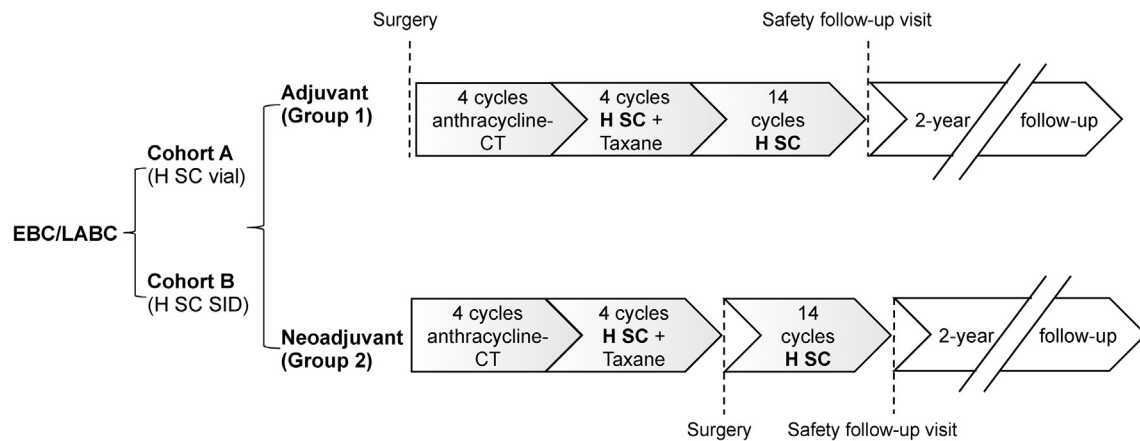


Fig. 1. Study design. The first 121 patients were assigned to cohort A and treated with H SC 600 mg/5 mL administered using a conventional syringe (vial), and the other 119 were assigned to cohort B and treated with H SC 600 mg/5 mL using an SID. In each cohort, patients were allocated to adjuvant (group 1) or neoadjuvant (group 2) treatment, based on the investigator's choice. In the adjuvant groups, CT was to start ≤ 10 weeks from definitive surgery. In the neoadjuvant groups, surgery of breast and axilla was planned after neoadjuvant CT and H SC, 3–4 weeks after the last CT cycle or until toxicity resolution. Taxane-based CT included weekly paclitaxel or docetaxel every 3 weeks. The 12-month H SC treatment period was followed by a 2-year observation period. EBC, early breast cancer; LABC, locally advanced breast cancer; H SC, subcutaneous trastuzumab; SID, single-use injection device; CT, chemotherapy.

was then administered as monotherapy every 3 weeks for the remaining 14 cycles. After 1 year of H SC treatment, patients entered a 2-year follow-up ending in April 2018.

In group 2, patients underwent conventional breast and axilla surgical procedures after neoadjuvant treatment.

The main objective of the present analysis was to describe the safety and tolerability of H SC (vial or SID) during the 1-year treatment period. Data on the patient and healthcare professional satisfaction are also reported. Other secondary objectives, including efficacy parameters and data collected during the 2-year follow-up, will be reported elsewhere.

The study was conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice. Approval from independent ethics committees and competent authority was obtained before starting the study.

2.2. Patient population

EBC/LABC patients, with HER2 positivity confirmed by the local assessment, were enrolled if they were aged ≥ 18 years; had no previous treatment for invasive malignancy; Eastern Cooperative Oncology Group performance status was 0–1; non-metastatic primary invasive adenocarcinoma of the breast was histologically confirmed; LVEF $\geq 55\%$ by echocardiography or multiple-gated acquisition scan before the first H SC dose and had intact skin at the injection site on the thigh.

The main exclusion criteria were a history of another malignancy, heart disease precluding the use of H, inadequate bone marrow, renal or hepatic function, concurrent enrolment in another clinical trial using an

investigational anticancer treatment, known hypersensitivity to the study drug or excipients or history of severe allergic reactions.

All patients provided written informed consent before enrolment.

2.3. Assessments

Treatment-emergent and serious AEs (hereafter AEs and SAEs, respectively) were recorded from the first H SC administration and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Safety laboratory assessments were performed, and vital signs were collected.

Standard laboratory examinations were carried out before each CT cycle, every four cycles during H monotherapy and at the safety follow-up visit, 28 days after the last dose.

Cardiac function was assessed at screening, H SC start, every 3 months afterwards, at the safety follow-up visit and every 6 months thereafter by evaluating the LVEF, electrocardiography (a standard 12-lead) and cardiac signs and symptoms. In case of LVEF decrease, the standard guidelines for cardiac toxicity management were adopted [15]. Finally, the patient and healthcare professional satisfaction was assessed by a patient satisfaction questionnaire (PSQ) in cohort B only and by a healthcare professional questionnaire (HCPQ) in both cohorts, respectively.

2.4. Statistical analysis

The safety end-points were analysed after all patients received 18 cycles of H SC and completed the post-treatment safety follow-up visit.

The sample size estimation was based on the LVEF rate, a safety end-point of primary interest. Assuming an observed LVEF $\geq$ grade 1 rate of 25%, an LVEF $\geq$ grade 2 of 4% and an LVEF $\geq$ grade 3 of 2%, a sample size of 240 would have produced a 95% confidence interval (CI) deemed sufficiently precise to draw valid conclusions around the event rate. The safety results within each cohort (vial and SID) were described without evaluating the differences between the two as this was not in the scope of this trial. The estimation of the CIs was performed using SAS, based on the Clopper-Pearson methodology.

The answers to PSQ and HCPQ were summarised using counts and percentages. Open questions were not summarised.

3. Results

3.1. Patients

Of 263 patients screened, 240 were enrolled in 52 Italian centres from December 2013 to October 2014: the first 121 patients were assigned to cohort A (vial) and the subsequent 119 to cohort B (SID). Patient disposition (intention-to-treat [ITT] population) is shown in Fig. 2. Overall, 201 patients completed the study treatment, and at the time of data cut-off, 110 patients in cohort A (90.9%) and 113 in cohort B (95.0%) had completed the

safety follow-up visit. Thirty-nine patients (16.3%) interrupted H SC before the end of the 18 cycles, the main reasons being intercurrent AEs (cohort A: N = 11, 9.1% and cohort B: N = 8, 6.7%).

All patients received a taxane-based CT regimen with weekly paclitaxel (81.7%) or docetaxel (18.3%).

Owing to sequential enrolment and lack of randomisation, there were minor differences in the baseline demographics, vital signs and cancer history between the two cohorts (Table 1, ITT population). Ten patients (8.3%) presented LA/inflammatory BC in cohort A and 13 (10.9%) in cohort B; the hormonal status was oestrogen receptor positive in 86 (71.1%) patients and 73 (61.3%), respectively, and/or progesterone receptor positive in 71 (58.7%) and 64 (53.8%), respectively.

At screening, patients in the neoadjuvant groups (N = 22 in each cohort) had larger tumours and a greater nodal involvement compared with the whole population (Table 1).

3.2. Primary analysis: safety and tolerability

Twelve patients were excluded from the safety population (N = 228) as they had not received H SC. Of 228 patients, 187 (82.0%) received adjuvant therapy (95/115 [82.6%] in cohort A and 92/113 [81.4%] in cohort B) and 41 (18.0%) received neoadjuvant therapy (20/115 [17.4%] and 21/113 [18.6%], respectively). As shown in Table 2,

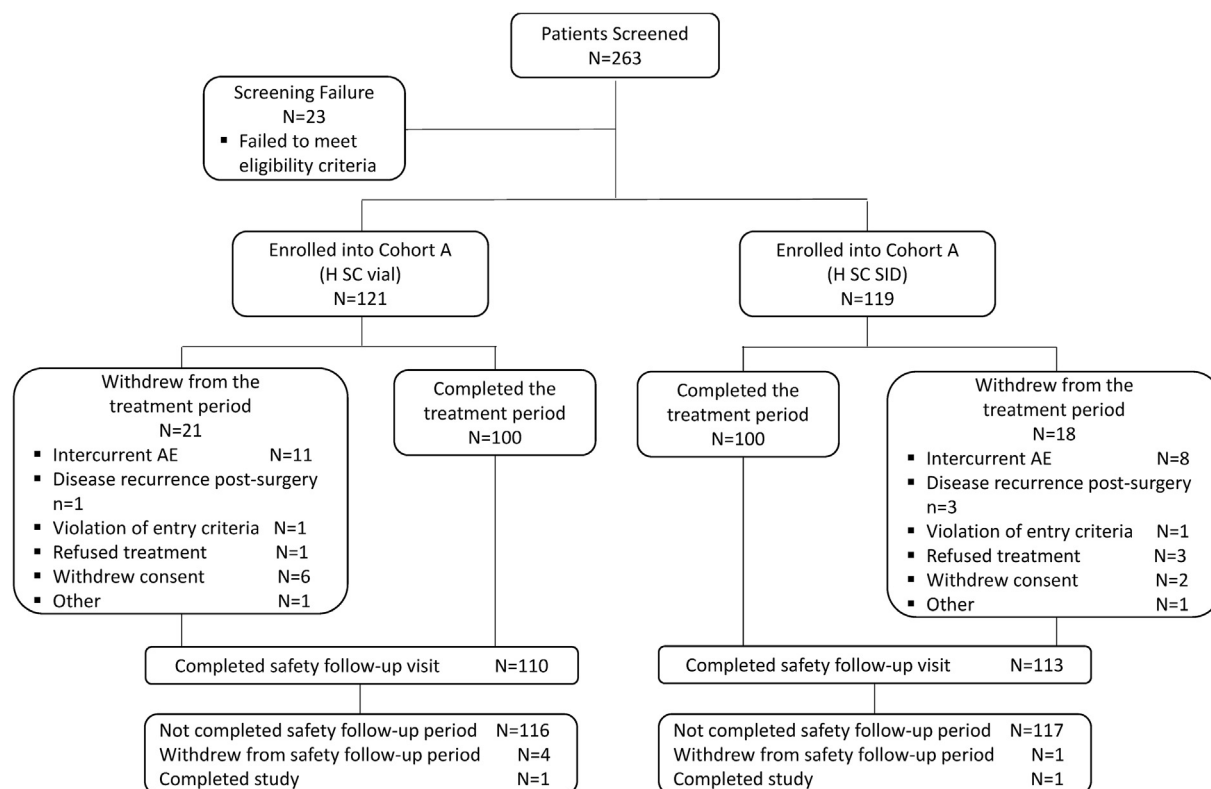


Fig. 2. Patient disposition (ITT population). H SC, subcutaneous trastuzumab; SID, single-use injection device; AE, adverse event; ITT, intention-to-treat.

Table 1
Patient demographics and tumour characteristics (ITT population).

Characteristic	Cohort A N = 121	Cohort B N = 119	Overall population N = 240	Overall neoadjuvant N = 44
Mean age at screening, yrs	55.1	53.2	54.2	
Menopausal status				
Premenopause	39 (33.1)	62 (52.1)	101 (42.1)	
Postmenopause	81 (66.9)	57 (47.9)	138 (57.5)	
Tumour location				
Left	64 (52.9)	53 (44.5)	117 (48.8)	
Right	56 (46.3)	66 (55.5)	122 (50.8)	
Missing	1 (0.8)	0	1 (0.4)	
T size				
Tis	0	0	0	
T1	59 (48.8)	47 (39.5)	106 (44.2)	3 (6.8)
T2	55 (45.4)	62 (52.1)	117 (48.7)	31 (70.5)
T3	4 (3.3)	6 (5.0)	10 (4.2)	5 (11.4)
T4	2 (1.7)	4 (3.4)	6 (2.5)	3 (6.8)
Missing	1 (0.8)	0	1 (0.4)	1 (2.3)
Nodal status				
N0	64 (52.9)	56 (47.1)	120 (50.0)	17 (38.6)
N1	38 (31.4)	43 (36.1)	81 (33.8)	22 (50.0)
N2+	18 (14.9)	19 (16.0)	37 (15.4)	4 (9.1)
Missing	1 (0.8)	1 (0.8)	2 (0.8)	1 (2.3)
Histological subtype				
Ductal	107 (88.4)	98 (82.4)	205 (85.4)	
Lobular	11 (9.1)	5 (4.2)	16 (6.7)	
Other	3 (2.5)	12 (10.1)	15 (6.3)	
Missing	0	4 (3.3)	4 (1.6)	
Histological grade				
Well differentiated	3 (2.5)	6 (5.0)	9 (3.7)	
Moderately differentiated	34 (28.1)	37 (31.1)	71 (29.6)	
Poorly differentiated	77 (63.6)	67 (56.3)	144 (60.0)	
Missing	7 (5.8)	9 (7.6)	16 (6.7)	
BC type				
Operable	111 (91.7)	106 (89.1)	217 (90.4)	
Locally advanced/inflammatory	10 (8.3)	13 (10.9)	23 (9.6)	
Hormonal status				
ER positive	86 (71.1)	73 (61.3)	159 (66.3)	
PgR positive	71 (58.7)	64 (53.8)	135 (56.3)	

ITT, intention-to-treat; SID, single-use injection device; BC, breast cancer; ER, oestrogen receptor; PgR, progesterone receptor.
Data are expressed as mean or frequency (N [%]).

224 patients (98.2%) experienced at least one AE from the beginning of anthracycline-based CT until the safety follow-up visit; from now on, only the AE/SAEs emerged after H SC start, including concomitant

administration of H SC with taxanes and H SC as monotherapy, will be considered.

High-grade AEs (grade 3–4) occurred in 61 patients (26.8%). The most commonly reported high-grade AEs not related to H SC treatment were neutropenia and decreased neutrophil count. Only nine patients (3.9%) had high-grade AEs considered as related to the study drug: erythema (N = 1), pain (N = 1), left ventricular systolic dysfunction (LVSD, N = 2), anaphylactic shock (N = 1), hypertension (N = 1), rash (N = 1), pleuropericarditis and mitral valve incompetence (N = 1) and tachycardia (N = 1). The related anaphylactic shock was observed in a 54-year-old patient during the third cycle of taxane plus H SC, and the SAE was resolved on the same day with antiallergic treatment.

In 17/228 (7.5%) patients, AEs led to the permanent H SC discontinuation, but they were deemed as related to H SC only in 12 cases (5.3%). The most frequent event class, occurring in eight cases (LVSD and

Table 2
Overall safety data obtained in the safety population.

Patients with at least one:	Cohort A N = 115	Cohort B N = 113	Overall N = 228
AE of any grade	114 (99.1)	110 (97.3)	224 (98.2)
Grade ≥ 3 AE	33 (28.7)	28 (24.8)	61 (26.8)
SAE	8 (7.0)	9 (8.0)	17 (7.5)
Death due to an AE	2 (1.7)	0 (0.0)	2 (0.9)

AE, adverse event; SAE, serious adverse event.

Data are presented as frequencies (N [%]) and were calculated relative to the total number of patients in the safety population.

An AE was any AE starting on the day of or after the first administration of the study drug and within 28 days after the last study drug. Grade ≥ 3 AEs included grade 3, 4, 5 and missing grade. Severity was assigned according to the National Cancer Institute Common Terminology Criteria for AEs, version 4.0.

decreased LVEF, N = 6; general cardiotoxicity, N = 1 and mitral valve incompetence, N = 1), was related to known H cardiotoxicity, while in other cases, to local and systemic infusion reactions (two anaphylactic shock, two erythema and one rash).

Overall, 17/228 patients (7.5%) experienced SAEs, which were considered as H SC related in 2/228 (0.9%) cases: anaphylactic shock (described previously) and pleuropericarditis.

Three patients died during the study, two owing to disease recurrence after cycle 4 and after the end of cycle 17 of H SC; the third patient, after completing 16 cycles of H SC therapy, was diagnosed with metastatic ovarian adenocarcinoma, which was considered as the cause of death.

3.3. Cardiac safety

Cardiac safety is summarised in Table 3. Forty-nine of 228 patients (21.5%) presented a cardiac-associated event of any grade, deemed as possibly related to treatment in 33 cases (14.5%). The most common AEs of suspected cardiac origin related to H SC were the following: decreased LVEF (N = 18, 7.9%), LV dysfunction (N = 5, 2.2%), tachycardia (N = 3, 1.3%), palpitations and chest pain (N = 2, 0.9%). Of these AEs, grade ≥ 3 events were identified only in 4/228 patients overall (1.8%) and SAEs in 2/228 (0.9%). At the time of data cut-off, three of the four events of grade ≥ 3 (i.e. two cases of ventricular dysfunction and one of pleuropericarditis) and both SAEs (i.e. 1 case of atrial fibrillation and 1 of pleuropericarditis) had resolved, while the case of mitral valve incompetence of grade ≥ 3 had not.

Table 3
Cardiac safety.

Patients with at least one:	Cohort A N = 115	Cohort B N = 113	Overall N = 228
AE of suspected cardiac origin (any grade)	29 (25.2)	20 (17.7)	49 (21.5)
SAE of suspected cardiac origin	2 (1.7)	0 (0.0)	2 (0.9)
AE suggestive of LVSD	9 (7.8)	5 (4.4)	14 (6.1)
SAE suggestive of LVSD	1 (0.9)	0 (0.0)	1 (0.4)
AE resulting in any LVEF decrease	18 (15.7)	10 (8.8)	28 (12.3)
SAE resulting in LVEF decrease	1 (0.9)	0 (0.0)	1 (0.4)
CHF	0 (0.0)	0 (0.0)	0 (0.0)

AE, adverse event; SAE, serious adverse event; LVSD, left ventricular systolic dysfunction; LVEF, left ventricular ejection fraction; CHF, congestive heart failure.

Data are presented as frequencies (N [%]) and were calculated relative to the total number of patients in the safety population.

An AE was any AE starting on the day of or after the first administration of the study drug and within 28 days after the last study drug. Grade ≥ 3 AEs included grade 3, 4, 5 and missing grade. Severity was assigned according to the National Cancer Institute Common Terminology Criteria for AEs, version 4.0.

Treatment-related AEs referred to AEs related to the study drug during the treatment period (i.e. cycles 1–18).

Fourteen of 228 patients (6.1%) experienced at least one AE of any grade that might be suggestive of LVSD, such as systolic dysfunction and rhythm alteration. Importantly, no cases of congestive HF (CHF) were observed.

From the screening to the safety follow-up visit, 23/228 patients (10.1%) experienced a relevant decline in LVEF ($\geq 10\%$ below the baseline and $< 50\%$). When considering the mean LVEF, a slight but consistent 2.9% reduction was described (Fig. 3), mainly occurring during the concurrent administration of taxanes and H SC.

3.4. Local and systemic infusion reactions

The frequency of systemic administration-related reactions (ARRs) and local injection site reactions (ISRs) potentially related to H SC was evaluated as previously described [11]. As shown in Table 4, 155/228 (68.0%) patients experienced ARR and 50/228 (21.9%) ISRs, but most of the reactions were mild or moderate (grade 1–2). The most frequent ARR and ISRs were pyrexia (N = 57, 25%) and pain (N = 15, 6.6%), respectively. Systemic ARR of grade ≥ 3 related to the study drug were reported in one case of erythema, one case of rash, one case of chest pain and one case of anaphylactic shock (already described), whereas severe ISRs related to H SC injection were observed in two cases of pain.

ARRs were more frequent, and ISRs were less frequent during taxane plus H SC than during H SC monotherapy. In patients treated with H SC only, no severe ISRs were reported.

3.5. Patient satisfaction questionnaire

Patient satisfaction was assessed among the patients of cohort B who had completed at least 14 cycles of the study drug, ten of which were self-administered using the SID (N = 19, 79.2%). Overall, most patients gave a positive feedback about the device (Fig. 4): they

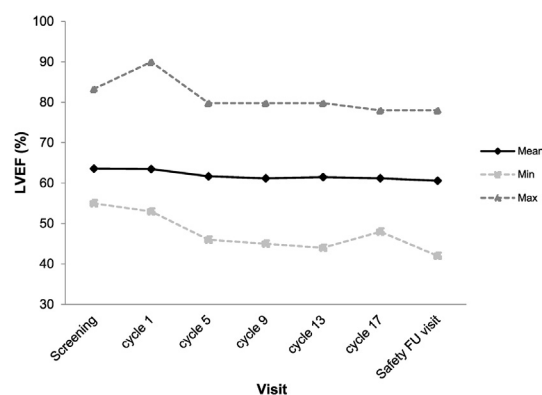


Fig. 3. Mean LVEF from the screening (N = 227) to the safety follow-up visit (N = 200). Dashed lines represent the minimum and maximum values. LVEF, left ventricular ejection fraction.

Table 4
Summary of systemic administration-related reactions (ARRs) and localised ISRs.

Reaction	Total patients	Patients with grade $\geq$ 3 reactions	IMP-related reactions	Related reactions cohort A	Related reactions cohort B
Systemic ARRs					
Erythema	46 (20.2)	1 (0.4)	4 (1.8)	3 (1.3)	1 (0.4)
Rash	16 (7.0)	1 (0.4)	4 (1.8)	0 (0.0)	4 (1.8)
Chest pain	16 (7.0)	1 (0.4)	3 (1.3)	2 (0.9)	1 (0.4)
Pruritus	15 (6.6)	0 (0.0)	3 (1.3)	1 (0.4)	3 (1.3)
Pyrexia	57 (25.0)	0 (0.0)	3 (1.3)	3 (1.3)	0 (0.0)
Chills	3 (1.3)	0 (0.0)	2 (0.9)	2 (0.9)	0 (0.0)
Anaphylactic shock	2 (0.9)	2 (0.9)	1 (0.4)	1 (0.4)	0 (0.0)
Localised ISRs					
Pain	15 (6.6)	1 (0.4)	3 (1.3)	2 (0.9)	1 (0.4)
Injection site erythema	3 (1.3)	0 (0.0)	3 (1.3)	3 (1.3)	0 (0.0)
Injection site reaction	3 (1.3)	0 (0.0)	3 (1.3)	2 (0.9)	1 (0.4)
Pain in extremity	21 (9.2)	1 (0.4)	1 (0.4)	1 (0.4)	0 (0.0)
Administration site oedema	1 (0.4)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)
Administration site pain	2 (0.9)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)
Injection site haematoma	1 (0.4)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)
Injection site pain	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)
Injection site pruritus	1 (0.4)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)
Subcutaneous abscess	2 (0.9)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)

IMP, investigational medicinal product; ISRs, injection site reactions; ARRs, administration-related reactions. Data are presented as frequencies (N [%]).

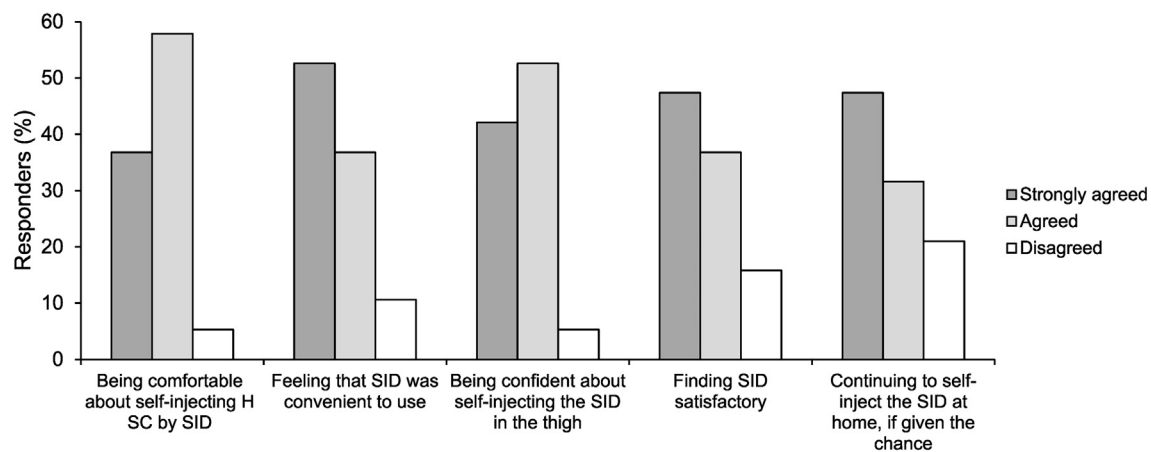


Fig. 4. Results of the PSQ. The questionnaire was filled in only by patients in cohort B (i.e. using the SID) who had completed at least 14 cycles of H SC and had self-administered at least ten cycles of H SC (N = 19, 79.2%). H SC, subcutaneous trastuzumab; SID, single-use injection device; PSQ, patient satisfaction questionnaire.

acknowledged to be comfortable about self-injection and felt that the SID was convenient to use, were confident about self-injecting H by the SID in the thigh and found the SID satisfactory. Moreover, if given the opportunity, most patients would continue to self-inject H SC via the SID at home.

3.6. Healthcare professional questionnaire

Investigators and nurses at each centre completed an HCPQ after at least four patients from their centre received ≥ 5 cycles of adjuvant treatment (Table 5). A total of 50 healthcare professionals completed the questionnaire in cohort B, most being oncology/CT nurses (N = 46, 92.0%). Overall, they claimed a

short time of delivery system preparation (<5 min for 36 [72.0%] responders), drug administration (<5 min for 28 [56.0%] and no longer than 15 min anyway) and overall hospital stay (<4 h for 45 [90%], the time being <2 h for 22 [44.0%]). Moreover, all responders acknowledged the possibility that H SC can simplify patient management and 48 responders [96.0%] acknowledged the convenience of H SC from the patients' point of view, regardless of the system used.

4. Discussion

The SCHEARLY study confirms the safety profile of H SC in patients with HER2-positive BC and the high

Table 5
Summary of the HCPQ provided to 50 healthcare professionals in cohort B.

Question	Cohort B N = 50
What is your primary speciality?	
Oncologist	8 (16.0)
Nurse	38 (76.0)
Other	4 (8.0)
Did you in person administer H SC during the study?	
Always	24 (48.0)
Sometimes	24 (48.0)
Never ^a	2 (4.0)
How long did it take to prepare the SID after receiving it from the pharmacy?	
<5 min	36 (72.0)
6–10 min	7 (14.0)
11–15 min	2 (4.0)
16–20 min	1 (2.0)
>20 min	4 (8.0)
How long did it take to position the SID and administer the drug?	
<3 min	13 (26.0)
<5 min	15 (30.0)
6–15 min	22 (44.0)
How many patients displayed at the injection site	
Rash	2 (4.0)
Many	18 (36.0)
Few	30 (60.0)
None	
Bruise	
Few	5 (10.0)
None	45 (90.0)
Infections	
None	50 (100.0)
Reactions correlated to SC injections ^b at the time of administration or immediately after?	
Few	7 (14.0)
None	43 (86.0)
How long did the patients stay in the hospital, on the days of H SC administration?	
<2 h	22 (44.0)
2–3 h	17 (34.0)
3–4 h	6 (12.0)
>4 h	5 (10.0)
How much anxiety did you think the patients experienced because of the SC administration?	
None	45 (90.0)
Enough	5 (10.0)
Overall, do you think that H SC may simplify patient management?	
Yes	50 (100.0)
No	0 (0.0)
If asked, would you suggest patients the SC over IV administration?	
Yes	48 (96.0)
No	2 (4.0)
If asked, would you suggest colleagues the SC over IV administration?	
Yes	45 (90.0)
No	4 (8.0)
Missing	1 (2.0)
Do you think that, from the patient point of view, SC administration was convenient?	
Yes	48 (96.0)
No	2 (4.0)

H, trastuzumab (Herceptin®); SC, subcutaneous; SID, single-use injection device; IV, intravenous; HCPQ, healthcare professional questionnaire. Data are reported as frequencies (N [%]).

^a In both cases, a specialised nurse did.

^b These included fever, chills, flu-like symptoms, skin rash, oedema of lips or face.

tolerability of this administration route, as demonstrated by the low number of severe infusion-related reactions [8,10,11].

Compared with the pivotal trials, the SCHEARLY trial had broader eligibility criteria and included patients

with HER2-positive LABC besides patients with EBC, setting a scenario similar to clinical practice. In this context, no novel safety issues emerged, and our findings confirm that H SC is a feasible option in patients with HER2-positive BC.

Overall, the present study detected a low rate of AEs leading to treatment discontinuation, consistent with the SafeHer study (7.5% vs 5.0%, respectively) [10]. Moreover, most of the AEs occurred during the administration of CT (alone or with H SC).

Cardiac dysfunction, including CHF and cardiotoxicity, is a clinically relevant AE associated with H IV [16,17], particularly following an anthracycline-based regimen [18]. Therefore, the AEs of suspected cardiac origin were strictly monitored during the treatment period. Notably, no CHF events were reported, which is a relevant finding because most patients received CT and H. Moreover, the rate of drug-related cardiac SAEs was low (0.9%) and comparable to that reported by the SafeHer study (high-grade cardiac SAEs: 0.9%) [10]. Cardiotoxicity was also low, with LVEF decreased in 10.1% of cases, by a mean of 2.9% from the baseline to the safety follow-up visit. Again, this result is consistent with previous reports.

The SC administration of H has been associated with local ISRs and systemic ARRs [11]. As expected, many patients experienced ISRs and ARRs in the SCHEARLY trial, but most reactions were mild/moderate and did not affect treatment. Overall, the rate of severe reactions (grade ≥ 3) was very low (0.4%). The apparently lower incidence of ISRs with the device deserves further investigations.

Most patients and healthcare professionals were satisfied with the self-injection using the SID, and the latter would have suggested the administration of H SC over H IV, irrespective of the device used. This is important, considering the disadvantages and negative influence of IV administration on patients' quality of life (QoL) [11,19].

At the time of study start, H SC was not commercially available. However, it is now widely used, and the lack of new safety issues along with the fact that both patients and healthcare professionals deemed it as advantageous over the IV formulation is reassuring.

In conclusion, the primary analysis of the SCHEARLY trial confirms the safety and tolerability of 600-mg H SC as adjuvant or neoadjuvant therapy in patients with HER2-positive EBC and indicates that this administration route might also be of interest for patients with LABC.

Conflict of interest statement

Montemurro F. received speaker's honoraria from Roche, AstraZeneca and Novartis and travel grants from Roche; Gori S. received honoraria from Eli Lilly; Iannacone C. as a biostatistician, received fees from Roche S.p.A., directly and through a contract research organization, for professional activities related to this article; Stell A. is a Roche employee and Gianni L. participated in advisory boards from Roche/GNE, GSK, Novartis, Synaffix and Synthron. The other authors have nothing to disclose.

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