Article type: Original article

Title: Efficacy and safety of subcutaneous trastuzumab and intravenous trastuzumab as part of adjuvant therapy for HER2-positive early breast cancer: Final analysis of the randomised, two-cohort PrefHer study

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Funding: This work was supported by F. Hoffmann-La Roche Ltd.

Word count: 2114/2500

References: 39/40

Figures and tables: 2 Figures, 5 Tables

Key words for indexing: breast cancer, HER2/neu, Herceptin, patient preference, subcutaneous, trastuzumab

Abstract

Aim: To assess efficacy (event-free survival, EFS) and safety in patients followed up for 3 years in the PrefHer study (NCT01401166).

Patients and methods: Post-surgery and -chemotherapy in the (neo)adjuvant setting, patients with HER2-positive early breast cancer were randomised to receive four cycles of the subcutaneous form of trastuzumab (Herceptin® SC [H SC] via single-use injection device [Cohort 1] or delivery via a hand-held syringe from an SC Vial [Cohort 2]; 600 mg fixed dose) followed by four of the intravenous form of trastuzumab (Herceptin® [H IV]; 8 mg/kg loading, 6 mg/kg maintenance doses) in the adjuvant setting, or vice versa, every 3 weeks. Patients could have received H before randomisation. H was then continued to complete a total of 18 cycles, including any cycles received before randomisation.

Results: A total of 488 patients were randomised across both cohorts. After median follow-up of 36.1 months, 3-year EFS across both groups in the evaluable intention-to-treat population (467 patients) was 90.6% overall, 89.9% in Cohort 1, and 91.1% in Cohort 2. No new safety signals were identified during long-term follow-up, with only one cardiac serious adverse event in the safety population (483 patients).

Conclusions: Three-year EFS data following H SC and H IV treatment are consistent with those reported by previous trials for H in the adjuvant setting. The overall safety profile during adjuvant treatment was as expected.

Word count: 226/250

1. Introduction

Trastuzumab (Herceptin® [H], F. Hoffmann-La Roche Ltd, Basel, Switzerland)-containing regimens are now standard of care for patients with HER2-positive breast cancer. A 600 mg fixed-dose manual injection of the subcutaneous form of H (Herceptin® SC [H SC], F. Hoffmann-La Roche Ltd), given via hand-held syringe from an H SC Vial, was approved following demonstrated non-inferiority compared with the intravenous form of H (H IV) based on pathological complete response and serum trough concentration in the HannaH study.[1] To date, over two million patients with breast cancer have been treated with H; approximately 80,000 of which were treated with H SC (F. Hoffmann-La Roche Ltd, data on file). The international, open-label, randomised, crossover PrefHer study (NCT01401166) investigated patient preference for H SC or H IV during the adjuvant treatment of HER2-positive early breast cancer. The study revealed overwhelming patient preferences for H SC (89%), regardless of the method of H SC delivery: single-use injection device (SID) or delivery via a hand-held syringe from an SC Vial, with ‘time saving’ and ‘less pain/discomfort/side effects’ the most common reasons given by the patients themselves during interviews.[2–4] There was a high preference for H SC irrespective of whether or not patients received H IV prior to study enrolment.[2,3] In addition, patients’ preferences for H SC for metastatic breast cancer have been demonstrated in the Metaspher study.[5] A time-and-motion study within the PrefHer study demonstrated a mean time saving of 55–57 min of patient chair time and 13–17 min of active healthcare professional time per session with H SC compared with H IV,[6] and several

countries have reported estimated increased hospital capacity and/or cost-savings with H SC.[7–17] These data support a transition to SC delivery.
We present efficacy and safety data after 3 years' follow-up in the PrefHer study.

2. Patients and Methods

2.1 Patients

Eligibility criteria have been described previously [2] and are available in the appendix.

2.2 Study design

Following surgery and completion of chemotherapy in the (neo)adjuvant setting, patients received four cycles of H SC (600 mg fixed dose injected over approximately 5 min into the thigh) every 3 weeks followed by four cycles of H IV (6 mg/kg) in the adjuvant setting, or vice versa (Fig. 1).[2] An H IV loading dose of 8 mg/kg was required only if the first cycle of study treatment was the initial IV dose of H (i.e., H IV/H SC); otherwise, the dose was 6 mg/kg every 3 weeks. Following these eight cycles (the crossover period), patients continued H SC or H IV therapy to complete 18 standard cycles (1 year) (H continuation period).

During crossover, patients in Cohort 1 received H SC via SID and patients in Cohort 2 received H SC via hand-held syringe from an H SC Vial.

Patients could have been either H-naïve (*de novo*) or could have already started H for early breast cancer prior to study entry (non-*de novo*), but

needed to receive at least eight more cycles to complete 1 year (18 cycles) of H in the adjuvant setting.

Following crossover, i.e. the H continuation period, it was planned for patients in Cohort 1 to receive H IV (unless choosing to self-administer H SC via SID), and for patients in Cohort 2 to receive H SC via hand-held syringe from an H SC Vial.

Following completion of H, patients were followed up for 3 years from randomisation (follow-up period).

The primary endpoint was patient preference (reported previously).[2,3] Secondary endpoints included event-free survival, safety and tolerability.

PrefHer was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All participating patients provided written informed consent. Approval for the protocol was obtained from appropriate local and national independent ethics committees.

2.3 Statistical considerations

EFS was assessed using the Kaplan–Meier approach and is presented for the overall evaluable intention-to-treat (ITT) populations (patients who completed the primary preference question and ≥1 administration of both H SC and H IV) for each cohort, and overall. EFS was defined as the time from randomisation to local, regional or distant disease recurrence, contralateral breast cancer or death from any cause.

Adverse events (AEs) and serious AEs (SAEs) were reported according to National Cancer Institute – Common Terminology Criteria for Adverse Events v4.0 and New York Heart Association criteria. Safety data are presented for

the overall safety population (patients who received at least one dose of study treatment) and by treatment period.

3. Results

3.1 Patients

The trial profile is shown in Supplementary Fig. 1. Four hundred and eighty-eight patients were randomised, 483 were included in the safety population, and 467 were included in the evaluable ITT population.[3] The *de novo* group comprised 98/483 patients (20.3%) and the non-*de novo* group 385/483 patients (79.7%). Four hundred and nine patients completed follow-up according to protocol. Baseline characteristics and treatment history are shown in Table 1 for the evaluable ITT population and Table 2 for the safety population.

3.2 EFS

After a median follow-up of 36.1 months (range 0–45.9 months), 3-year EFS across both randomisation groups in the overall evaluable ITT population was 90.6% overall (95% confidence interval [CI] 87.4–92.9%) (Fig. 2A), 89.9% in Cohort 1 (95% CI 84.9–93.3%) (Fig. 2B), and 91.1% in Cohort 2 (95% CI 86.6–94.2%) (Fig. 2C). Overall, 46/467 patients (9.9%) had an EFS event by the end of follow-up: 16/467 (3.4%) had a local occurrence, 8/467 (1.7%) a regional occurrence, 30/467 (6.4%) a distant recurrence and 3/467 (0.6%) had contralateral breast cancer (patients could have been counted in more than one event-type but only once overall).

3.3 Safety

Taking into account the H cycles received prior to randomisation, 425/483 (88.0%) patients in the safety population received all 18 H cycles, with a median of 13 on-study. The majority of patients in the *de novo* group (89/98, 90.8%) completed all 18 H cycles and, taking into account cycles received before randomisation, the majority of non-*de novo* patients (336/385, 87.3%) also completed all 18 H cycles. Forty-three patients in Cohort 1 received H SC by SID during the continuation period, with the remainder receiving H IV. In Cohort 2, ten patients chose to receive H IV during the continuation period, with the remainder receiving H SC via hand-held syringe from an H SC Vial. Among the 58/483 patients (12.0%) in the safety population who discontinued treatment before the end of the planned 18 cycles, the most common reasons for treatment discontinuation were adverse events (22 patients, 4.6%) and disease recurrence (14 patients, 2.9%). No deaths occurred on-treatment. A total of 409 patients completed follow-up, including 30 of the patients who had previously discontinued treatment.

The most common AEs of any grade were arthralgia (13.7%), asthenia (13.7%) and headache (10.4%) (Table 1). No other AEs occurred in ≥10% of patients (Table 3). Differences in AE rates between H SC and H IV periods during crossover (Table 4) were driven by injection site reactions, and rates were similar between H SC and H IV periods when injection site reactions were excluded (275/479 [57.4%] and 258/478 [54.0%], respectively).

Most AEs were grades 1 or 2, with grade 3 events in 45 patients (9.3%) (Table 4). No grade 4 or 5 AEs were reported. AEs considered by the investigator to be related to H treatment were reported in 213 patients (44.1%),

and at grade 3 severity in 14 patients (2.9%). Left ventricular dysfunction and dyspnoea (two patients each) were the only H-related grade 3 AEs that occurred in more than one patient.

SAEs were reported in 19/483 patients (3.9%) (Table 4). Only one (left ventricular dysfunction in one Cohort 2 patient during the H SC continuation period) was considered by the investigator to be related to H treatment. This resulted in temporary discontinuation of study drug; the patient recovered completely. All SAEs had resolved by clinical cut-off.

AEs resulted in treatment discontinuation in 21/483 patients (4.3%), 7/244 (2.9%) in Cohort 1 and 14/239 (5.9%) in Cohort 2. Left ventricular dysfunction (one patient in Cohort 1 and six in Cohort 2), congestive cardiac failure (one patient in Cohort 1 and two in Cohort 2) and injection site pain (two patients in Cohort 2) were the only AEs that led to discontinuation in more than one patient. There were eight deaths during the study, two in Cohort 1 and six in Cohort 2. All were attributed to disease recurrence.

3.4 Cardiac AEs

A total of 49 cardiac AEs were reported in 40/483 patients (8.3%), with left ventricular dysfunction (11 patients, 2.3%), palpitations (seven patients, 1.4%), ejection fraction decreased (seven patients, 1.4%), congestive cardiac failure (five patients, 1.0%), bradycardia (three patients, 0.6%) and extrasystoles (two patients, 0.4%) being the only cardiac AEs occurring in more than one patient (Table 5). Most cardiac events were grades 1 and 2, with only one cardiac SAE (left ventricular dysfunction; described above). Only four patients had grade 3 cardiac events; three experienced left ventricular dysfunction

(one in Cohort 1, two in Cohort 2) and one patient in Cohort 2 experienced congestive heart failure. No patients experienced serious congestive heart failure.

4. Discussion

The PrefHer study demonstrated an overwhelming patient preference (89%) for treatment with H SC over H IV during the adjuvant treatment of HER2-positive early breast cancer, regardless of the method of H SC delivery (SID or delivery via a hand-held syringe from an SC Vial,[2,3]) with clear and meaningful benefits in time saving for both patients and healthcare professionals in addition to patient-reported advantages of convenience and less pain/discomfort/side effects.[2–4] SC delivery of a 600 mg fixed dose was shown to result in non-inferior trough H serum concentrations and pathological complete response compared with body-weight-based IV dosing in the HannaH study.[1] EFS was also similar between H SC and H IV after 2 years of treatment-free follow-up.[18] Recently, studies including HannaH showed that pathological complete response was associated with EFS.[18–20] In the current report we describe 3-year efficacy and safety of H SC in the PrefHer study.

Overall, the 3-year EFS rates following H SC and H IV treatment observed in both cohorts were consistent with efficacy observed in previous clinical trials of adjuvant H therapy for patients with HER2-positive early breast cancer.[21–24]

Previous safety analyses of PrefHer, which were limited to the crossover period, have indicated that H SC was well tolerated, with no new safety

signals identified,[2,3] and that safety was not affected by switching from H IV to H SC or vice versa.[25] The 3-year results of PrefHer presented here confirm these findings. No additional safety signals were identified and safety was as expected during the crossover periods and H continuation periods in both cohorts. Long-term analyses of cardiac events in phase III trials of H show that late congestive heart failure is uncommon, with most events occurring during treatment, and that the majority of cardiac events are reversible.[26–33] Our data are consistent with these findings, with few grade 3 cardiac AEs and only one cardiac SAE in 483 patients. There were no associations between cardiac safety and method of delivery (SID or hand-held syringe from an H SC Vial) or phase of treatment during the trial.

A limitation of the current study is that, because patients received both H IV and H SC and may have switched between the two on one or more occasions, analysis of subgroups, e.g. by body weight, would be difficult to interpret, and therefore these have not been performed. Previous studies, however, have shown that the efficacy and safety of H SC is comparable in patients of low and high body weight.[1,18,34]

H remains a key component of treatment for HER2-positive breast cancer, both in the (neo)adjuvant and metastatic settings. Recent long-term data from the NeoSphere and APHINITY studies were of particular interest, as they suggested a progression-free and (invasive) disease-free survival benefit of combining anti-HER2 therapies (pertuzumab and H) with chemotherapy in the neoadjuvant and adjuvant settings, respectively.[20,35] The survival benefit of H plus pertuzumab and docetaxel is also proven in the metastatic setting.[36,37] Combining pertuzumab with H SC may provide further benefits

and convenience for patients in the future and the safety profile of this combination in metastatic breast cancer has been reported in the phase IIb SAPPHIRE study [38] and the phase III MetaPHER study.[39] However, as observed in PrefHer [2, 3], a small proportion of patients prefer H IV and can ask for it.

In conclusion, 3-year EFS results following H SC and H IV treatment confirm efficacy findings from previous trials of H in the adjuvant setting. H SC was well tolerated and no new safety signals were identified compared with the known profiles of H IV or H SC from previous reports in HER2-positive early breast cancer.

Acknowledgements

We thank the individuals who contributed to the design of the study instruments, the patients, their families, the nurses, the interviewers and the investigators who participated in this study.

Funding for the PrefHer study was provided by F. Hoffmann-La Roche Ltd. Support for third-party writing assistance for this manuscript, furnished by John Carron, PhD, of Health Interactions, was provided by F. Hoffmann-La Roche Ltd.

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Figures and tables

Table 1 – Patient characteristics (evaluable ITT population).

[a] Denominator = 116. [b] Denominator = 117.[c] Denominator = 116.

[d] Denominator = 110. [e] Denominator = 459.

Abbreviations: H, trastuzumab (Herceptin®); ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; SC, subcutaneous.

	Cohort 1		**Cohort 2**		
	H SC→ H IV *n* = 117	**H IV→ H SC *n* = 119**	**H SC→ H IV *n* = 118**	**H IV→ H SC *n* = 113**	**Overall *N* = 467**
Median age, years (range)	54.0 (32–76)	51.0 (28–75)	50.0 (29–78)	53.0 (27–76)	52.0 (27–78)
Median weight, kg (range)	68.6 (35.0–12.0)[a]	66.0 (45.0–131.8)[b]	67.5 (49.0–103.8)[c]	65.5 (41.0–117.0)[d]	67.0 (35.0–131.8)[e]
Oestrogen receptor status, n (%)					
Negative	39 (33.3)	40 (33.6)	40 (33.9)	41 (36.3)	160 (34.3)
Positive	77 (65.8)	79 (66.4)	74 (62.7)	71 (62.8)	301 (64.5)
Unknown	1 (0.9)	0	4 (3.4)	1 (0.9)	6 (1.3)
ECOG PS at screening, n (%)					
0	95 (81.2)	96 (80.7)	99 (83.9)	91 (80.5)	381 (81.6)
1	22 (18.8)	23 (19.3)	19 (16.1)	21 (18.6)	85 (18.2)
Not done	0	0	0	1 (0.9)	1 (0.2)
TNM classification at diagnosis, n (%)					
T0	1 (0.9)	3 (2.5)	0	1 (0.9)	5 (1.1)
T1	62 (53.0)	40 (33.6)	47 (39.8)	51 (45.1)	200 (42.8)
T2	38 (32.5)	57 (47.9)	61 (51.7)	43 (38.1)	199 (42.6)
T3	8 (6.8)	11 (9.2)	5 (4.2)	12 (10.6)	36 (7.7)
T4	6 (5.1)	8 (6.7)	3 (2.5)	6 (5.3)	23 (4.9)
Not assessable/ unknown	2 (1.7)	0	2 (1.7)	0	4 (0.9)
Lymph node-positive at diagnosis, n (%)	48 (41.0)	66 (55.5)	61 (51.7)	53 (46.9)	228 (48.8)
H before enrolment, n (%)					
De novo	27 (23.1)	27 (22.7)	20 (16.9)	20 (17.7)	94 (20.1)
Non-*de novo*	90 (76.9)	92 (77.3)	98 (83.1)	93 (82.3)	373 (79.9)
Previous treatment, n (%)					
Chemotherapy	117 (100)	119 (100)	117 (99.2)	113 (100)	466 (99.8)
Radiotherapy	75 (64.1)	74 (62.2)	71 (60.2)	68 (60.2)	288 (61.7)
Hormonal therapy	50 (42.7)	52 (43.7)	48 (40.7)	44 (38.9)	194 (41.5)
Lapatinib	0	1 (0.8)	0	1 (0.9)	2 (0.4)

Table 2 – Patient characteristics (safety population).

[a] Denominator = 121. [b] Denominator = 120.[c] Denominator = 119.

[d] Denominator = 115. [e] Denominator = 475.

Abbreviations: H, trastuzumab (Herceptin®); ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; SC, subcutaneous.

	Cohort 1		**Cohort 2**		
	H SC→ H IV ***n* = 122**	**H IV→ H SC** ***n* = 122**	**H SC→ H IV** ***n* = 121**	**H IV→ H SC** ***n* = 118**	**Overall** ***N* = 483**
Median age, years (range)	55.0 (32–83)	51.0 (28–75)	50.0 (29–78)	53.0 (27–76)	53.0 (27–83)
Median weight, kg (range)	69.0 (35.0–120.0)[a]	65.7 (45.0–131.8)[b]	67.0 (49.0–103.8)[c]	66.0 (41.0–117.0)[d]	67.0 (35.0–131.8)[e]
Oestrogen receptor status, n (%)					
Negative	44 (36.1)	40 (32.8)	40 (33.1)	44 (37.3)	168 (34.8)
Positive	77 (63.1)	82 (67.2)	77 (63.6)	73 (61.9)	309 (64.0)
Unknown	1 (0.8)	0	4 (3.3)	1 (0.8)	6 (1.2)
ECOG PS at screening, n (%)					
0	97 (79.5)	98 (80.3)	102 (84.3)	93 (78.8)	390 (80.7)
1	25 (20.5)	24 (19.7)	19 (15.7)	14 (20.3)	92 (19.0)
Not done	0	0	0	1 (0.8)	1 (0.2)
TNM classification at diagnosis, n (%)					
T0	1 (0.8)	3 (2.5)	0	1 (0.8)	5 (1.0)
T1	64 (52.5)	41 (33.6)	48 (39.7)	51 (43.2)	204 (42.2)
T2	40 (32.8)	59 (48.4)	63 (52.1)	46 (39.0)	208 (43.1)
T3	8 (6.6)	11 (9.0)	5 (4.1)	13 (11.0)	37 (7.7)
T4	7 (5.7)	8 (6.6)	3 (2.5)	7 (5.9)	25 (5.2)
Not assessable/ unknown	2 (1.6)	0	2 (1.7)	0	4 (0.8)
Lymph node-positive at diagnosis, n (%)	51 (41.8)	67 (54.9)	63 (52.1)	57 (48.3)	238 (49.3)
H before enrolment, n (%)					
De novo	28 (23.0)	29 (23.8)	21 (17.4)	20 (16.9)	98 (20.3)
Non-*de novo*	94 (77.0)	93 (76.2)	100 (82.6)	98 (83.1)	385 (79.7)
Previous treatment, n (%)					
Chemotherapy	122 (100)	122 (100)	120 (99.2)	118 (100)	482 (99.8)
Radiotherapy	76 (62.3)	76 (62.3)	73 (60.3)	70 (59.3)	295 (61.1)
Hormonal therapy	50 (41.0)	55 (45.1)	50 (41.3)	45 (38.1)	200 (41.4)
Lapatinib	0	1 (0.8)	1 (0.8)	1 (0.8)	3 (0.6)

Table 3 – Adverse events in ≥5% patients in any period (safety population). [a] Could be counted once per grade but ≥ once overall.

Abbreviations: AE, adverse event; H, trastuzumab (Herceptin®); IV, intravenous; SC, subcutaneous; SID, single-use injection device.

	Crossover			Continuation		Overall
Patients, *n* (%)[a]	**H SC period *n* = 479**	**H IV period *n* = 478**	***P* value (H SC period vs. H IV period)**	**H IV or H SC (syringe) *n* = 440**	**H SC (SID) *n* = 43**	***N* = 483**
Any AE	300 (62.6)	258 (54.0)	0.01	223 (50.7)	12 (27.9)	388 (80.3)
Arthralgia	25 (5.2)	27 (5.6)	0.78	22 (5.0)	1 (2.3)	66 (13.7)
Asthenia	30 (6.3)	25 (5.2)	0.58	20 (4.5)	0	66 (13.7)
Headache	20 (4.2)	17 (3.6)	0.74	21 (4.8)	0	50 (10.4)
Hot flush	22 (4.6)	17 (3.6)	0.51	8 (1.8)	1 (2.3)	45 (9.3)
Fatigue	19 (4.0)	18 (3.8)	1.00	13 (3.0)	0	44 (9.1)
Nausea	25 (5.2)	14 (2.9)	0.10	9 (2.0)	1 (2.3)	39 (8.1)
Injection site pain	32 (6.7)	0	<0.01	6 (1.4)	2 (4.7)	37 (7.7)
Diarrhoea	16 (3.3)	12 (2.5)	0.57	12 (2.7)	0	35 (7.2)
Pain in extremity	19 (4.0)	7 (1.5)	0.03	8 (1.8)	0	31 (6.4)
Injection site erythema	28 (5.8)	0	<0.01	4 (0.9)	0	30 (6.2)
Injection site reaction	29 (6.1)	0	<0.01	2 (0.5)	0	29 (6.0)
Nasopharyngitis	11 (2.3)	10 (2.1)	1.00	12 (2.7)	1 (2.3)	29 (6.0)
Erythema	17 (3.5)	6 (1.3)	0.03	7 (1.6)	1 (2.3)	26 (5.4)

Table 4 – Adverse event profile (safety population). [a] Could be counted once per grade but ≥ once overall.

Abbreviations: AE, adverse event; H, trastuzumab (Herceptin®); IV, intravenous; SC, subcutaneous; SAE, serious adverse event; SID, single-use injection device.

	Crossover			**Continuation**		**Overall**
Patients with ≥ 1 AE, *n* (%)[a]	**H SC period *n* = 479**	**H IV period *n* = 478**	***P* value (H SC period vs. H IV period)**	**H IV or H SC (syringe) *n* = 440**	**H SC (SID) *n* = 43**	***N* = 483**
Median H cycles, *n*	4.0	4.0	–	5.0	2.0	13.0
Any AE	300 (62.6)	258 (54.0)	0.01	223 (50.7)	12 (27.9)	388 (80.3)
Grade 1	262 (54.7)	206 (43.1)	<0.01	175 (39.8)	10 (23.3)	360 (74.5)
Grade 2	119 (24.8)	110 (23.0)	0.54	85 (19.3)	5 (11.6)	214 (44.3)
Grade 3	17 (3.5)	16 (3.3)	1.00	16 (3.6)	1 (2.3)	45 (9.3)
Grade 4	0	0	–	0	0	0
Grade 5	0	0	–	0	0	0
AE with suspected causal relationship to study medication	163 (34.0)	53 (11.1)	<0.01	60 (13.6)	4 (9.3)	207 (42.9)
Discontinuation for AE	5 (1.0)	6 (1.3)	0.77	10 (2.3)	0	21 (4.3)
Any SAE	4 (0.8)	4 (0.8)	1.00	11 (2.5)	1 (2.3)	19 (3.9)
Treatment-related SAE	0	0	–	1 (0.2)	0	1 (0.2)

Table 5 – Cardiac adverse events (safety population). [a] Could be counted once per grade but ≥ once overall. [b] Cardiac disorders not listed: bradycardia (three patients), extrasystoles (two patients), angina pectoris, cardiomyopathy, diastolic dysfunction, heart valve incompetence, left ventricular hypertrophy, mitral valve incompetence, sinus bradycardia, tachycardia (one patient each). [c] Ejection fraction decreased (seven patients), ejection fraction abnormal, electrocardiogram change (one patient each).

Abbreviations: AE, adverse event; H, trastuzumab (Herceptin®); IV, intravenous; SC, subcutaneous; SID, single-use injection device.

	Crossover		**Continuation**		**Overall**
Patients with ≥ 1 AE, *n* (%)[a]	**H SC period *n* = 479**	**H IV period *n* = 478**	**H IV or H SC (syringe) *n* = 440**	**H SC (SID) *n* = 43**	***n* = 483**
Any cardiac AE	12 (2.5)	15 (3.1)	17 (3.9)	0	40 (8.3)
Grade 1	9 (1.9)	11 (2.3)	11 (2.5)	0	28 (5.8)
Grade 2	2 (0.4)	3 (0.6)	6 (1.4)	0	10 (2.1)
Grade 3	1 (0.2)	2 (0.4)	1 (0.2)	0	4 (0.8)
Cardiac disorders (any grade)[b]	8 (1.7)	14 (2.9)	14 (3.2)	0	33 (6.8)
Left ventricular dysfunction	2 (0.4)	5 (1.0)	4 (0.9)	0	11 (2.3)
Palpitations	3 (0.6)	2 (0.4)	2 (0.5)	0	7 (1.4)
Congestive heart failure	2 (0.4)	0	3 (0.7)	0	5 (1.0)
Investigations (any grade)[c]	4 (0.8)	3 (0.6)	3 (0.7)	0	9 (1.9)