A US trial to compare the efficacy, safety and immunogenicity of subcutaneous HX575 (proposed biosimilar epoetin alfa) with the reference medicine in the treatment of anemia associated with chronic kidney disease

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ABSTRACT

Background

HX575 (biosimilar epoetin alfa) was approved in Europe in 2007 for the treatment of chronic kidney disease (CKD)-related anemia. This study assessed clinical equivalence of HX575 with the US-licensed reference medicine (Epogen®/Procrit®, Amgen/Janssen) following subcutaneous (SC) administration in dialysis patients with anemia of CKD.

Methods

This was a randomized, double-blind, parallel-group, multicenter study (NCT01693029) conducted at 49 US clinical sites. Eligible patients were aged ≥18 years, had end-stage renal disease, were on hemodialysis or peritoneal dialysis for ≥6 months (or ≥12 months in the case of a failed kidney transplant), and were receiving treatment with stable SC doses of the reference medicine. Eligible patients also had mean hemoglobin (Hb) concentration between 9.0 and 11.5 g/dL during the screening period. The primary endpoint was the mean absolute change in Hb concentration between the screening/baseline period (week -4 to -1) and the evaluation period (week 21 to 28).

Results

Hb values at the end of the evaluation period and the Hb change from baseline to evaluation period were similar between treatment groups. The estimated difference between groups in mean absolute change in Hb concentration was -0.093 g/dL, with 90% CI (-0.23, 0.04) entirely within the pre-specified equivalence limits (-0.5, 0.5 g/dL). The safety profile of each medicine was similar and as expected in dialysis patients, and neither treatment led to the development of neutralizing, clinically relevant antibodies.

Conclusions

SC HX575 in dialysis patients with renal anemia was therapeutically equivalent to the reference medicine in terms of maintaining stable Hb levels.

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INTRODUCTION

HX575 (biosimilar epoetin alfa; Binocrit®, Hexal AG) was approved in Europe in 2007 for the treatment of chronic kidney disease (CKD)-related anemia. The initial approval of HX575 was for intravenous (IV) administration, which was in accordance with the label of the reference medicine at that time. More recently, a multinational, open-label, single-arm, phase III European study was conducted to evaluate the safety and immunogenicity of subcutaneous (SC) HX575 in CKD-related anemia in pre-dialysis and dialysis patients [Casadevall et al 2017]. SC use of HX575 was found to be well tolerated and stable hemoglobin (Hb) levels were maintained. Based on these data, the SC administration of HX575 was approved by the European Commission in March 2016 [Binocrit® SmPC].

Here we report the results of a randomized, double-blind, efficacy and safety study (the ACCESS study, A Clinical Research Study in Chronic Kidney Disease & Anemia) conducted in the United States (US), which aimed to show clinical equivalence of HX575 with the US-licensed reference medicine (Epogen®/Procrit®, Amgen/Janssen) following SC administration in dialysis patients with anemia of CKD.

METHODS

The study was a randomized, double-blind, parallel-group, multicenter study (NCT01693029) in which patients were enrolled at 49 US clinical sites. The relevant Institutional Review Boards approved the protocol and the trial was conducted in accordance with the Declaration of Helsinki International Council for Harmonisation (ICH)

Good Clinical Practice and any applicable local regulations. All analyzed patients provided written, informed consent.

Male and female patients aged 18 years or older were eligible if they had end-stage renal disease and were on hemodialysis or peritoneal dialysis for at least 6 months (or at least 12 months in the case of a failed kidney transplant). All patients had to be receiving treatment with stable (≤30% change in weekly dose during screening) SC doses of the reference medicine administered at least once per week, with a maximum weekly dose of 300 IU/kg. Eligible patients had mean Hb concentration between 9.0 and 11.5 g/dL during the screening period (samples were taken prior to the dialysis session, preferably in the middle of the week), and had adequate iron substitution (serum ferritin ≥200 µg/L and transferrin saturation ≥20%, confirmed by a sample taken at first screening).

Main exclusion criteria included history of pure red cell aplasia (PRCA) or anti-erythropoietin antibodies; lack of efficacy or loss of effect with a previous erythropoiesis-stimulating agent (ESA) therapy; historical or current positive result for binding anti-erythropoietin antibodies. Eligibility was assessed during a 4-week screening period, after which patients entered a 52-week treatment period.

Study design

Patients were randomized 1:1 by an interactive response technology to SC HX575 or reference medicine. During treatment, the dose was individually titrated to maintain Hb levels in the target range 10.0–11.0 g/dL. The primary endpoint was the mean absolute change in Hb concentration between the screening/baseline period (week -4 to -1) and the evaluation period (week 21 to 28). The primary analysis was performed in the intention to treat (ITT) population, which consisted of all randomized patients who were exposed to treatment with study drug for ≥4 weeks and had ≥1 Hb value available at week 4 or later. The estimated difference in Hb level between the groups was determined by analysis of covariance (ANCOVA). Treatment was included as a factor and the covariates were mean

baseline Hb and mean weekly dose during the evaluation period. HX575 would be considered equivalent to the reference medicine if the two-sided 90% confidence intervals (CI) resided entirely within the equivalence limits of -0.5 g/dL to 0.5 g/dL. It was planned to randomize at least 360 patients to maintain at least 320 evaluable patients (randomized 1:1 to HX575 and the reference medicine) to have 90% power to reject the null hypothesis that the treatment with HX575 was not equivalent to the reference medicine.

Secondary endpoints included the incidence of antibody formation against epoetin (anti-erythropoietin binding antibodies and neutralizing antibodies), overall safety profiles, and epoetin dose. The safety population consisted of all patients who were randomized and received ≥1 dose of study drug. The evaluation of the immune response was based on a validated, highly sensitive anti-erythropoietin antibody-binding radioimmunoprecipitation (RIP) assay and validated cell-based neutralizing antibody assays performed at the sponsor's laboratory.

RESULTS

A total of 835 patients were screened, of whom 437 were randomized (Supplemental material, Figure S1). Two patients were treated but excluded from any analyses due to informed consent issues; the remaining 435 comprised the safety population. In total, 210 patients treated with HX575 and 212 patients treated with the reference medicine were included in the ITT population and were analyzed for the primary endpoint.

Baseline demographic and clinical characteristics were similar between the treatment groups (Table 1). Overall, mean (standard deviation [SD]) age was 58.7 (13.6) years and 57.5% of patients were male. The primary cause of CKD was diabetes (HX575, 53.0%; reference medicine, 56.0%), followed by hypertension (HX575, 30.0%; reference medicine, 23.9%) and chronic glomerulonephritis (HX575, 6.0%; reference medicine, 7.3%).

Efficacy

At baseline, mean (SD) Hb concentration was 10.53 (0.64) g/dL in the HX575 group and 10.50 (0.62) g/dL in the reference medicine group (Table 2). Hb values at the end of the evaluation period and the Hb change from baseline to evaluation period were similar between treatment groups (Table 2 and Figure 1). The estimated difference between groups in mean absolute change in Hb concentration was -0.093 g/dL, with 90% CI (-0.23, 0.04) entirely within the pre-specified equivalence limits (-0.5, 0.5 g/dL), therefore the primary endpoint of the study was met.

Epoetin dose

The mean (SD) epoetin dose in the HX575 group was 7761 (9488) IU at week 1, 5877 (5786) IU during the evaluation period (week 21–28), and 6054 (8381) IU at week 52. For the reference group, the mean (SD) epoetin dose was 6662 (6447) IU at week 1, 5840 (6065) IU during the evaluation period (week 21–28), and 4440 (5315) IU at week 52. The mean weekly epoetin dose tended to be higher in the HX575 group than in the reference group; this difference was present at the beginning of the study (i.e. after conversion from the pre-study ESA treatment) and the trend continued throughout the study.

Safety

The most frequently reported TEAEs were hypertension (HX575, 11.5%; reference medicine 13.3%), diarrhea (HX575, 10.1%; reference medicine, 8.7%), hyperkalemia (both groups, 9.2%), and nausea (HX575, 7.8%; reference medicine, 9.6%). In total, 5 (2.3%) patients in the HX575 group and 11 (5.0%) in the reference group reported TEAEs considered by investigators to be related to the study drug (Supplemental material, Table S1).

Four (0.9%) patients experienced five treatment-emergent serious AEs (SAEs) that were considered related to treatment. In the HX575 group, three (1.4%) patients experienced four related treatment-emergent SAEs (cerebrovascular accident, ischemic stroke,

myocardial infarction, and worsening of anemia), while in the reference group, there was one (0.5%) case of congestive cardiac failure considered related to treatment. Thromboembolic events and *de-novo* malignancies were categorized as TEAEs of special interest. The incidence of thromboembolic events was similar between the two treatment groups (HX575, 35 [16.1%] patients and 45 events; reference medicine, 36 [16.5%] patients and 54 events). Malignancies were reported more frequently for the reference medicine group (9 patients [4.1%] versus 4 patients (1.8%) in the HX575 treatment group), however, the absolute number of events was very low in general (10 versus 4 events, respectively). Five patients in the HX575 group and 11 in the reference medicine group died during the treatment phase (up to 30 days after last dose) due to TEAEs. In both treatment groups, the most common TEAEs leading to death were conditions associated with the System Organ Class *Cardiac Disorders* (n=5 in each group). The other TEAEs leading to death in the reference medicine group where chronic renal failure, azotemia, endocarditis/cerebrovascular accident, bladder cancer, acute respiratory failure and cachexia (all n=1). No causal relationship with the study drug was suspected in any of the TEAEs leading to death.

Immunogenicity

Nine patients tested positive for binding anti-erythropoietin antibodies by RIP assay (Table 3; 7 patients in the HX575 group and 2 in the reference group). This includes two patients (one patient from each treatment arm) who were already RIP-positive at baseline, prior to which all patients had been receiving pre-study treatment with the reference medicine. Both of these patients tested negative at the first screening assessment but positive at the baseline assessment (sample taken before any administration of study drug), and were discontinued (as per protocol) when the results of the baseline assessment became available. Treatment-emergent binding anti-erythropoietin antibodies were detected in 7 patients (6 [2.8%] in the HX575 group and 1 [0.5%] in the reference group); treatment

duration-related incidence rates of anti-erythropoietin antibodies were 0.036 (HX575) and 0.011 (reference medicine; Table 4). The titers of RIP anti-erythropoietin antibodies were low and fluctuating, and all 7 patients who tested positive in the RIP assay at one point during the study had at least one subsequent negative RIP assay result. None of these patients developed neutralizing anti-erythropoietin antibodies at any time.

The occurrence of binding but non-neutralizing anti-erythropoietin antibodies was not found to be associated with AEs during the study period and for 30 days following study discontinuation, nor to have any impact on efficacy in the study period and the subsequent safety follow-up. There were no clinical signs of immunogenicity or hypersensitivity during the 12-month treatment period.

DISCUSSION

The double-blind, comparative ACCESS study met its primary objective and demonstrated that SC administration of HX575 in patients on dialysis with renal anemia was therapeutically equivalent to the reference medicine administered SC in terms of maintaining stable Hb levels. In addition to comparable efficacy, HX575 and the reference medicine demonstrated a similar safety profile, which was also consistent with that expected for epoetin alfa in patients on dialysis. Furthermore, SC administration of HX575 or the reference medicine did not elicit the development of neutralizing or otherwise clinically relevant antibodies during the 12-month study period and during the subsequent safety follow-up (at least 6 months).

These findings are consistent with those from an open-label single-arm, phase III European study, which found that SC HX575 maintained stable Hb levels in 416 dialysis- and non-dialysis-dependent adult patients with CKD [Casadevall et al 2017]. Also in the European study, no patient developed neutralizing antibodies and anti-erythropoietin antibodies were mainly transient despite the fact that all patients who tested positive for anti-drug

antibodies remained in the study and continued treatment with SC HX575. In contrast, patients in the ACCESS study were discontinued if they tested positive in the RIP assay, in accordance with the study protocol.

The proportion of patients in ACCESS who tested positive for anti-erythropoietin antibodies after study drug administration is similar to that in the European SENSE study [Casadevall et al 2017]; it is also consistent with other data from the literature on the development of binding, non-neutralizing antibodies following ESA treatment in clinical studies [Barger et al 2012]. In ACCESS, the titers of RIP anti-erythropoietin antibodies were low and fluctuating. All 7 patients who tested positive in the RIP assay at one point during the study had at least one subsequent negative RIP assay result, and some patients alternated between positive and negative RIP assay results. These observations, together with the highly sensitive RIP assay used (a potential 1% false-positive rate), indicate that there was no sustained, clinically relevant anti-drug antibody response in any patient.

An earlier comparative renal anemia study of SC HX575 using pre-filled syringes ended prematurely following the occurrence of two cases of neutralizing antibodies [Haag-Weber et al 2012]. A thorough root-cause analysis identified aggregate formation due to increased tungsten levels [Seidl et al 2012]; the source of these elevated tungsten levels was the heat-resistant tungsten pins used to manufacture the glass syringes. A switch to special low-tungsten syringes eliminated this risk and reduced the immune potential of HX575, as evidenced in the SENSE study [Casadevall et al 2017]. In the ACCESS study, medication was provided in single-dose vials (consistent with the US-approved reference medicine) and had never been in contact with tungsten.

In the current ACCESS study, patients randomized to HX575 received a slightly higher starting dose than those randomized to the reference medicine, and this trend continued throughout the study treatment period. The double-blind nature of the study treatment excludes the role of investigator bias in administering higher doses in the HX575 arm from

the start. The higher doses of HX575 throughout the study treatment period are unlikely to be due to decreased effectiveness compared with the reference medicine, given that the dose difference was evident from the start of treatment. There is also no evidence of a dose penalty when switching to biosimilar ESAs, based on other published data. A large (n=1695 patients with CKD) post-approval study of HX575 administered IV was conducted to monitor AEs in clinical practice, and also assessed the efficacy of HX575 after conversion from a range of pre-study ESAs [Hörl et al 2012]. Target Hb levels were maintained effectively after patients were switched to IV HX575. The dose of HX575 was stable in those patients switched from previous IV ESA treatment, with a significant (but expected) 13% dose increase in patients switched from prior SC ESA treatment. Another study investigated differences between originator and biosimilar ESA utilization based on defined daily doses (DDD), doses upon switching, differences between short- and long-acting ESAs and prescribed daily doses (PDD) in ambulatory patients (n=6117) with renal anemia undergoing chronic maintenance hemodialysis [Hörbrand et al 2013]. In this population-based analysis of real-world data, doses were not increased when the therapy was switched from the originator to the biosimilar ESA. Moreover, in 1,886 patients receiving a continuous prescription over 12 accounting quarters, patients receiving short-acting originator ESAs, long-acting darbepoetin alfa and biosimilar ESAs had a similar median daily DDD consumption (0.80, 0.86 and 0.81, respectively) [Hörbrand et al 2013].

In summary, SC administration of HX575 in patients on dialysis with renal anemia was therapeutically equivalent to the reference medicine in terms of maintaining stable Hb levels. SC administration of HX575 and the reference medicine was well tolerated, and the safety profile of each was similar and as expected in patients on dialysis. SC administration of HX575 and the reference medicine did not elicit the development of neutralizing, clinically relevant antibodies during the 12-month study period and the 6-month safety follow-up period.

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DISCLOSURES

Dr Weir has acted as a scientific advisor for Sandoz and Akebia.

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Table 1. Patient demographics and baseline characteristics (safety population)

Parameter		HX575 N=217	Reference epoetin alfa N=218
Age, years	mean (SD)	59.8 (13.76)	57.6 (13.40)
	min, max	23, 90	24, 89
Sex, n (%)	Male	135 (62.2)	115 (52.8)
	Female	82 (37.8)	103 (47.2)
Race, n (%)	Caucasian	139 (64.1)	128 (58.7)
	Black or African American	57 (26.3)	72 (33.0)
	Asian	6 (2.8)	13 (6.0)
	Other*	15 (6.9)	5 (2.3)
Height, cm	mean (SD)	167.2 (10.17)	166.0 (10.33)
	min, max	132, 201	142, 203
Weight, kg	mean (SD)	82.8 (20.75)	86.5 (24.32)
	min, max	41, 146	44, 178
BMI, kg/m^2	mean (SD)	29.55 (6.872)	31.41 (8.783)
	min, max	17.6, 49.1	16.9, 69.9
Time since start of dialysis, months	mean (SD)	51.14 (49.93)	55.62 (60.14)
Method of dialysis at baseline, n (%)	Hemodialysis	192 (88.5)	192 (88.1)

	Peritoneal dialysis	25 (11.5)	26 (11.9)
Time since start of ESA therapy, months	mean (SD)	40.72 (38.22)	48.38 (50.59)
Receiving iron therapy**, n (%)		72 (33.2)	70 (32.1)

*other race includes “American Indian or Alaska native”, “Native Hawaiian or other Pacific Islander”

**prior to first administration of study drug

BMI = body mass index, ESA = erythropoiesis-stimulating agent, SD = standard deviation

Table 2. Hemoglobin levels (ITT population)

		Hb level, g/dL				
Treatment group	**Time point**	**Mean**	**SD**	**min, max**	**LS Mean**	**SE**
HX575 N=210	Baseline period	10.53	0.635	8.4, 12.5		
	Evaluation period	10.42	0.826	7.1, 12.8		
	Change from baseline to evaluation period	-0.11	1.001	-3.1, 2.8	-0.0960	0.0575
Reference epoetin alfa N=212	Baseline period	10.50	0.615	8.3, 11.8		
	Evaluation period	10.51	0.873	7.8, 12.5		
	Change from baseline to evaluation period	0.01	0.953	-2.8, 2.5	-0.0035	0.0573

Hb=hemoglobin; ITT=intention-to-treat; LS=least squares; SD=standard deviation; SE=standard error

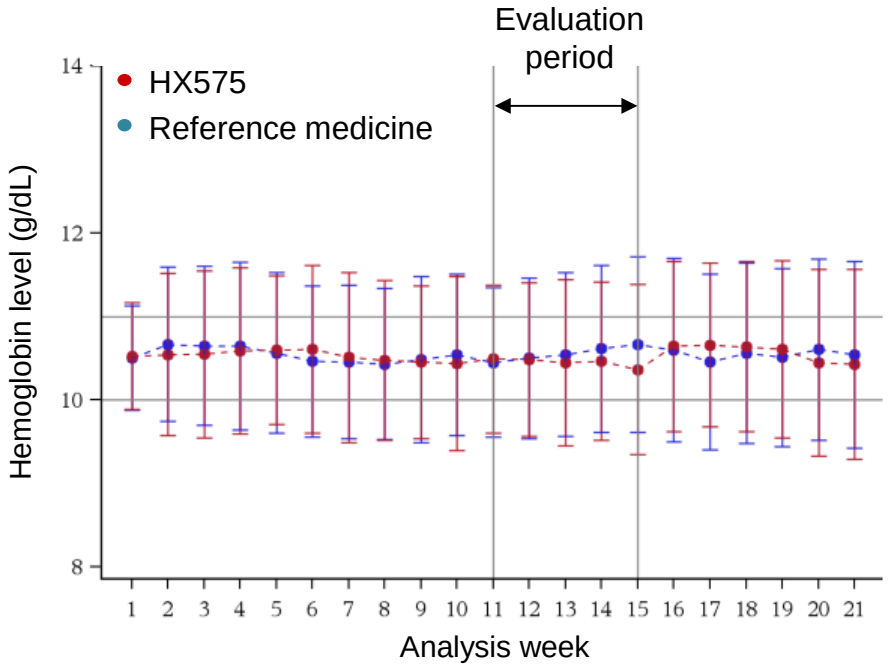
Table 3. Incidence of antibody formation against erythropoietin during the treatment period (safety population)

Treatment group	Assay	Patients with any result, n	Patients with a positive result, n	Percent (95% CI)	Incidence rate related to treatment duration
HX575 N=217	RIP	214	7	3.3 (1.3, 6.6)	0.036
	NAb	7	0	-	-
Reference epoetin alfa N=218	RIP	216	2	0.9 (0.1, 3.3)	0.011
	NAb	2	0	-	-

CI=confidence interval; NAb=neutralizing antibody; RIP=radioimmunoprecipitation

Two patients (1 in each group) were already RIP-positive at baseline prior to study treatment

Figure 1. Mean (SD) Hb levels over time (ITT population)



Hb=hemoglobin; ITT=intention-to-treat; SD=standard deviation

Supplemental material

Figure S1. Patient disposition

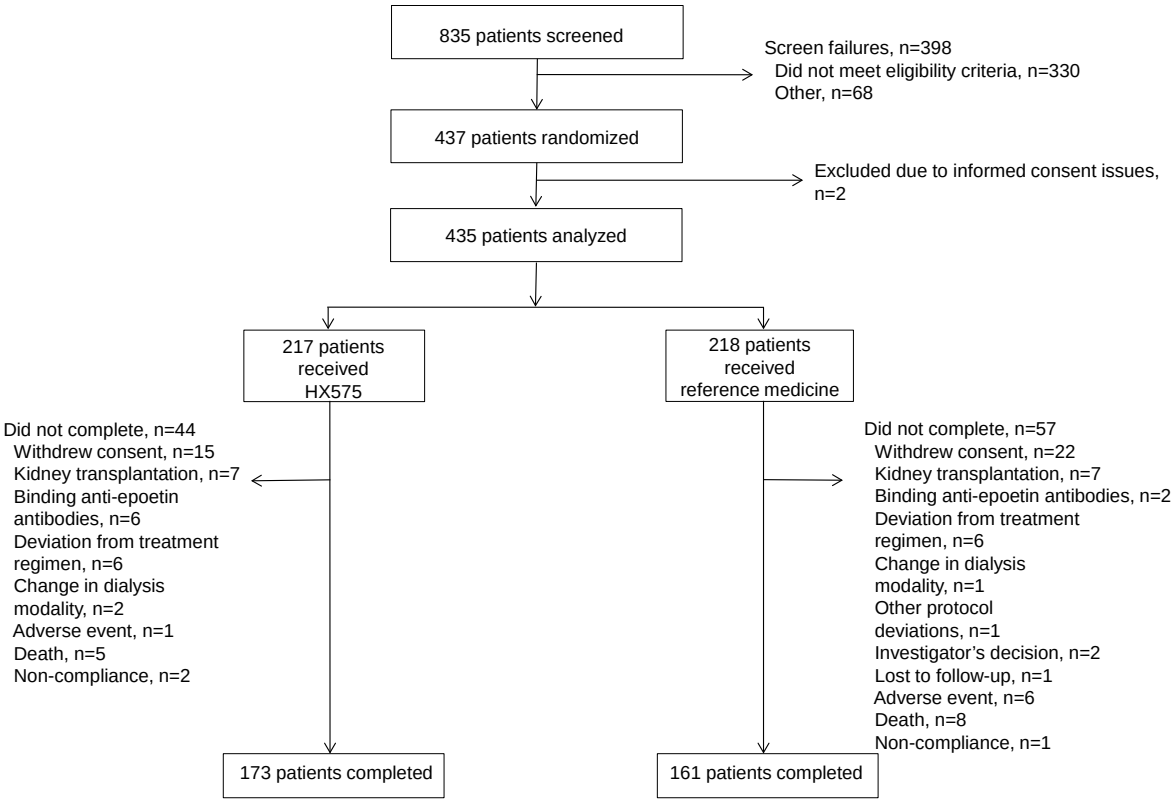


Table S1. Overview of treatment-emergent adverse events (safety population)

	HX575 N=217 n (%) E	Reference epoetin alfa N=218 n (%) E
TEAE	178 (82.0) 1078	185 (84.9) 1347
Drug-related	5 (2.3) 6	11 (5.0) 12
Serious	91 (41.9) 211	90 (41.3) 265
Drug-related serious	3 (1.4) 4	1 (0.5) 1
Special interest events	39 (18.0) 49	44 (20.2) 64
Thromboembolic events	35 (16.1) 45	36 (16.5) 54
Malignancies	4 (1.8) 4	9 (4.1) 10
Study-drug discontinuation	5 (2.3) 5	14 (6.4) 14
Death	5 (2.3) 5	11 (5.0) 12

E=number of events; n=number of patients; TEAE=treatment-emergent adverse event