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Biopharmaceuticals Clinical Development

Epoetin alfa

Non-interventional Clinical Study Report HX575-507

Title	Multicenter non-interventional post-authorization safety study (NI-PASS) to monitor the incidence of relevant and expected rare adverse events including lack of efficacy among CKD patients receiving s.c. Binocrit® or Epoetin alfa HEXAL®
Version identifier of the final study report	Final V1.0
Date of final study report	19-Oct-2023 (content final)
EU PAS register number	EUPAS14525
Active substance	HX575 epoetin alfa Pharmacotherapeutic group: other anti-anemic preparations ATC code: B03XA01
Medicinal product	Binocrit®/Epoetin alfa HEXAL®
Product reference	EU/1/07/410/001-055, EU/1/07/411/001-055
Procedure number	EMEA/H/C/725-727/MEA13.5.x (procedure number not yet assigned)
Marketing authorization holder(s)	Sandoz GmbH, Biochemiestrasse 10, 6250 Kundl, Austria and Hexal AG, Industriestrasse 25, 83607 Holzkirchen, Germany and Medice Arzneimittel Pütter GmbH & Co KG, Kuhloweg 37, 58638 Iserlohn, Germany
Joint PASS	No
Research questions and objectives	The purpose of this NI-PASS was to increase the dataset on the safe use of s.c. HX575 by extending the safety database of patients with chronic kidney disease (CKD)-induced anemia who received s.c.

	HX575 treatment and by monitoring closely the adverse event (AE) profile under real-life post-approval conditions. The primary study objective was to assess the incidence of relevant and expected rare AEs (defined as AEs of Special Interest [AESIs]) in response to HX575 s.c. treatment in patients with CKD-induced anemia.
Countries of study	Bulgaria, Croatia, Germany, Greece, Italy, Poland, Romania, Slovakia, Slovenia, and Spain

Marketing authorization holders

Marketing authorization holders	**European Union:** Sandoz GmbH Biochemiestrasse 10 6250 Kundl Austria Hexal AG Industriestrasse 25 83607 Holzkirchen Germany Medice Arzneimittel Pütter GmbH & Co KG Kuhloweg 37 58638 Iserlohn Germany
MAH contact person	PPD PPD Regulatory Affairs Sandoz Biopharmaceuticals Sandoz GmbH Biochemiestrasse 10 6250 Kundl Austria Phone: PPD Email: PPD

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1 Abstract

Title	Multicenter non-interventional post-authorization safety study (NI-PASS) to monitor the incidence of relevant and expected rare adverse events including lack of efficacy among CKD patients receiving s.c. Binocrit® or Epoetin alfa HEXAL® Date: 19-Oct-2023 (content final) Author: PPD PPD Sandoz Biopharmaceuticals
Keywords	Adverse events (AE), chronic kidney disease (CKD), epoetin alfa, lack of efficacy (LOE), pure red cell aplasia (PRCA), NI-PASS
Rationale and background	Binocrit®, Epoetin alfa HEXAL® (collectively called HX575) and Abseamed® have been authorized as biosimilars since 28-Aug-2007 in the EU for the intravenous (i.v.) route of administration in patients with anemia due to CKD. Since 31-Mar-2016 it has also been authorized for the subcutaneous (s.c.) route of administration in CKD patients. This non-interventional study was conducted to address a post-authorization requirement to evaluate the safety profile of HX575 administered s.c. in patients with CKD-induced anemia, under real-life conditions in order to increase confidence on the safe use of s.c. HX575. Since Sandoz's epoetin alfa is marketed under 3 different brand names, the study outcome data are therefore also representative for Abseamed® although only patients treated with Binocrit® and Epoetin alfa HEXAL® were included in this study.
Research question and objectives	The purpose of this category 3 non-interventional post-authorization safety (NI-PASS) study was to increase the dataset on the safe use of s.c. HX575 by extending the safety database of the product in patients with CKD-induced anemia, who received s.c. HX575 treatment and by monitoring closely the AE profile under real-life post-approval conditions. The primary study objective was to assess the incidence of relevant and expected rare AEs (defined as AEs of Special Interest [AESIs]) in response to HX575 s.c. treatment in patients with CKD-induced anemia. The estimated (i.e. anticipated at the time of protocol writing) incidence rate (IR) of rare drug-related AEs was ≤ 0.1%. Secondary objectives of this NI-PASS study were to assess and to monitor the general safety, tolerability, and effectiveness of s.c. HX575 treatment in patients with CKD-induced anemia.

Study design	This was an observational (i.e. non-interventional), multi-center, open-label, single arm NI-PASS in patients treated for CKD-induced anemia, with or without dialysis. In this study, commercially available s.c. HX575 was used as prescribed per the treating physician's best clinical judgment for CKD-induced anemia. This NI-PASS did not impose any mandatory treatment regimens and did not require assessment of specific tests by the treating physician. Eligible patients consenting to participate in the study were to be enrolled into the study earliest 1 day after initiation of s.c. HX575. Data were to be documented at specified data collection time points, i.e. at the time of enrollment into the study (Visit 1, V1), after 4, 8, 12, 16 and 20 months (V2-V6) and at the end of the individual observation period (EOS) after 24 months or at premature discontinuation.
Setting	129 hospitals and individual practices from 10 European countries (Bulgaria, Croatia, Germany, Greece, Italy, Poland, Romania, Slovakia, Slovenia, and Spain) The actual enrolment for this study took place from 10-Apr-2017 (enrolment of first patient) to 06-Nov-2020 (enrolment of last patient). Data were collected from 12-Apr-2017 (Start of data collection) to 08-Feb-2023 (End of data collection corresponding to data base lock).
Subjects and study size, including dropouts	Patients of both genders aged ≥ 18 years with CKD-induced anemia with or without dialysis treatment who were on chronic HX575 s.c. treatment or who just recently commenced HX575 s.c. treatment (i.e. who had started s.c. HX575 at least 1 day prior to provision of informed consent) were eligible for this study. Patients with known primary LOE to a recombinant erythropoietin/erythropoietin/erythropoiesis stimulating agent (ESA) product, a history of treatment with an erythropoietin/ESA product not authorized in the EU, or a history of anti-epoetin antibodies were to be excluded. Approximately 2500 adult patients with CKD were planned to be enrolled, and a total of 2510 eligible patients were actually enrolled. The planned duration of the observation period per patient was 24 months.
Variables and data sources	As this was a non-interventional study, the following variables were collected, as long as they were available in the patients' medical records and were part of standard of care: • Demographics (age, gender, weight, height) • Relevant medical history • Concomitant medications (in particular previous use of ESA) • Hematology parameters • Dialysis modalities • Iron status/supplementation • Transfusions • AEs: verbatim, evaluation of fulfillment of criteria for AE of Special Interest, start and end date, outcome, intensity, action taken, relationship to study drug, seriousness • Anti-epoetin antibody assessments (particular in case of reported LOE) • End of study data (completion status, completion date, last administration date for s.c. HX575, reason for discontinuation)

	When determination of anti-epoetin antibodies was considered clinically warranted by the treating physician, Hexal AG offered the possibility of sending appropriately collected patient serum taken in accordance with clinical routine practice and standard of care to the bioanalytical laboratory of Hexal AG, Oberhaching, Germany, for a highly sensitive assessment of presence of the anti-epoetin antibodies (and, in case of a positive binding anti-drug antibody (ADA) result, subsequent testing for anti-epoetin neutralizing antibodies). Since the patients have been treated and managed according to routine clinical practice, determination of anti-epoetin antibodies could have been performed also at local laboratories. Data were collected in an electronic case report form (eCRF). The eCRFs were reviewed for any inconsistencies and when necessary, queries were raised. Key collected data were verified against the source data. Data sources were the patients' medical records. In some cases, when certain information was not recorded in the source documents (e.g. inclusion/exclusion criteria, medical history start/end dates, primary mechanism of chronic kidney disease etc.) as per the study site's usual clinical practices, part of the eCRF served as source documentation. In these cases, a document was available at the study site clearly identifying those data fields that were recorded directly in the eCRF, and for which the eCRF stood as the source document.
Results	**Disposition** Of the 2510 enrolled patients, 2497 patients (99.5%) received s.c. HX575 and were included in the SAF: 1334 patients (53.1%) completed the study and 1176 patients (46.9%) were discontinued from the study as per investigator decision. The most common reasons for discontinuation of patients from the study were death in 476 patients (40.5%), lost to follow up in 170 patients (14.5%), switch from s.c. to i.v. treatment in 104 patients (8.8%), and patient´s condition no longer required study treatment in 85 patients (7.2%).“Other” reasons (like transplantation, changed nephrology site, patient decision, start of hemodialysis, etc.) led to study discontinuation in 124 patients (10.5%). **Documented patient years** Overall, the study monitored the safety of s.c. HX575 treatment in 2497 CKD patients for a median time of 1.83 years covering a total of 3600.2 patient years (SAF population). **Demographics and baseline characteristics** All following analyses are based on the SAF (N=2497): There were slightly more male (55.7%) than female patients (44.3%). The mean (std) age was 69.7 (13.93) years. The majority (85.7%) of patients had a vascular disorder and more than half (56.0%) had a metabolism and nutrition disorder; cardiac disorders were reported in 41.9% of patients and renal and urinary disorders in 32.7% of patients. At baseline, most patients had Stage 3, Stage 4, or Stage 5 CKD, with approximately half (52.5%) of the patients having Stage 5 CKD. Less than half of the patients were on dialysis (1090 patients [43.7%]) at baseline. Of these, most were on hemodialysis (959 patients [88.0%]).

	Primary endpoint **PRCA** No patient experienced PRCA. **Lack of Efficacy** Lack of efficacy was reported in 1 patient. The recorded details of this case and the Sponsor's assessment were as follows: This patient started treatment with s.c. HX575 in September 2017 and was enrolled in the study on 23-Apr-2018. The LOE was reported 7 days after the patient's start in the study. During the time when LOE was reported, the patient was suffering from gastric hemorrhage which resulted in blood loss and anemia (decrease in hemoglobin). The investigator did not collect blood for ADA assessment. The LOE event resolved in 2018 (at an unrecorded date). The s.c. HX575 was discontinued from Day 82 (13-Jul-2018) to Day 112 (12-Aug-2018). The interruption of s.c. HX575 was approximately 3 months after LOE was reported. The reason for interruption was not available. Reticulocyte count and iron/transferrin saturation were not available. The patient did not receive any transfusion or prior iron supplementation. Ferritin levels showed a decline at 25 ng/mL on Day 101 (1-Aug-2018) which later on increased to 82 ng/mL on Day 228 (6-Dec-2018). The patient resumed study treatment and the dose was increased from 5 kIU QW to 10 kIU BIW. The patient completed the study on 09-Apr-2020. **Sponsor's assessment:** The Sponsor's medical experts did not consider this as a confirmed LOE case, as the cause of the decrease in hemoglobin values was due to foregoing blood loss. Moreover, after an interruption of approximately 1 month, HX575 treatment was resumed and was effective for the remainder of study. **Major thromboembolic and cardiovascular events, congestive heart failure, and hypertension** The most frequently reported AESIs were major thromboembolic and cardiovascular events in 6.5% of patients with an IR (per 1000 patient years) of 46 (95% CI: 39, 53), congestive heart failure in 4.8% of patients with an IR of 33 (95% CI: 27, 39), and hypertension (worsening or newly developing hypertension, hypertensive crisis, uncontrolled hypertension) in 2.0% of patients with an IR of 13 (95% CI: 10, 18). **Seizures** Seizures were reported in 0.2% of patients with an IR (per 1000 patient years) of 1 (95% CI: 1, 3). **Blood disorder (white blood cell lineage disorders, thrombocythemia and porphyria)** Blood disorders were reported in 0.4% of patients with an IR (per 1000 patient years) of 2 (95% CI: 1, 5). **De-novo malignancies, unexpected tumor growth** De-novo malignancies or unexpected tumor growth were reported in 3.2% of patients with an IR (per 1000 patient years) of 22 (95% CI: 18, 27). **Hypersensitivity reactions, anaphylaxis incl. serious skin reactions**

	Hypersensitivity reactions, anaphylaxis incl. serious skin reactions were reported in 0.1% of patients with an IR (per 1000 patient years) of 1 (95% CI: <1, 3). **Hyperkalemia** Hyperkalemia was reported in 2.8% of patients with an IR (per 1000 patient years) of 19 (95% CI: 15, 24). **Posterior reversible encephalopathy syndrome** No patient experienced posterior reversible encephalopathy syndrome. **Secondary endpoints** **Incidence of SAEs** Overall, SAEs were reported in 893 patients (35.8%) with an IR (per 1000 patient years) of 279 (95% CI: 261, 298). The most frequently reported SAEs by PT were death (with no reported reason) with an IR (per 1000 patient years) of 34 (95% CI: 29, 41); pneumonia with an IR of 19 (95% CI: 15, 24); and cardiac failure with an IR of 18 (95% CI: 14, 22). **Incidence of AEs** Overall, AEs were reported in 1300 patients (52.1%) with an IR (per 1000 patient years) of 482 (95% CI: 456, 509). Mild AEs were reported with a highest IR of 214 (95% CI: 198, 231) compared to moderate (157 [95% CI: 144, 171]) or severe (176 [95% CI: 163, 191]) AEs. The most frequently reported AEs by PT were death (with no reported reason) with an IR (per 1000 patient years) of 34 (95% CI: 29, 41); pneumonia with an IR of 20 (95% CI: 16, 25); anemia with an IR of 19 (95% CI: 15, 24); and COVID-19 and hyperkalemia with an IR of 19 (95% CI: 15, 24). The most frequently reported AEs by PT related to s.c. HX575 was hypertension with an IR (per 1000 patient years) of 2 (95% CI: 1, 4). In total, 483 (19.3%) deaths were reported in the study. The most frequently reported AEs leading to death by PTs were death (with no reported reason with an IR (per 1000 patient years) of 34 (95% CI: 29, 41); sepsis with an IR of 12 (95% CI: 9, 16); and pneumonia with an IR of 9 (95% CI: 7, 13). **Number of patients discontinuing the study prematurely and reasons for discontinuations** Overall, 88 patients (3.5% [95% CI: 2.8, 4.3]) reported any AEs leading to discontinuation of s.c. HX575 treatment. SAEs leading to s.c. HX575 discontinuation were reported in 72 patients (2.9% [95% CI: 2.3, 3.6]). The most common reasons for discontinuation of patients from the study were death in 476 patients (40.5%), lost to follow up in 170 patients (14.5%), switch from s.c. to i.v. treatment in 104 patients (8.8%), and patient´s condition no longer required study treatment in 85 patients (7.2%).“Other” reasons (like transplantation, changed nephrology site, patient decision, start of hemodialysis, etc) led to study discontinuation in 124 patients (10.5%), **Red blood hematology parameters over time: hemoglobin concentration, red blood cells (RBC), absolute and relative reticulocyte count, hematocrit** Overall, red blood hematology parameters (hemoglobin concentration, RBC, absolute and relative reticulocyte counts, and hematocrit) over time

	remained stable (Visit 1 to Visit 7) in all the patients. Target hemoglobin levels (10 g/dL to 12 g/dL) were achieved and maintained during Visit 1 to Visit 7 (as specified in SmPC reference) and hematocrit levels were in the target range (30% to 36% per SmPC) in all the patients. **Number of patients receiving transfusions** A total of 148 patients received one or more transfusions during the study. No meaningful differences in the mean values of other hematology parameters by visits (Visit 1 to Visit 7) were observed in the study. Whereas there was slight improvement in the mean values for across the study visits (data collection time points every 4 months), the mean transferrin saturation remained stable (Visit 1 to Visit 7). More than half of the patients (1740 [69.7%]) received iron supplementation during the study. **Weekly epoetin dosage over time** Mean (std) weekly epoetin dosage received by patients ranged from 99.12 (84.063) IU/kg at Visit 1 to 94.24 (84.405) IU/kg at Visit 7 which was within the range as specified in the SmPC. **Other Data:** **Dialysis** A total of 1090 patients (43.7%) were on any type of dialysis at the time of Visit 1; most of these patients (959 [88.0%]) were on hemodialysis. **Immunogenicity** There were 2 patients who underwent ADA testing: One patient underwent anti-epoetin antibody testing due to decreased hemoglobin on Day 115 (PPD), after receiving s.c. HX575 for approximately 4 months. Hemoglobin, ferritin, and transferrin saturation levels for the patient were 8.3 g/dL (decrease of 2.5 g/dL; 10.8 g/dL at previous visit [Visit 1]), 487 ng/mL, and 19%, respectively. Assessments for reticulocytopenia and bone marrow biopsy were not performed. Since the ADA test result was negative, anti-epoetin antibody induced PRCA was ruled out. Decreased hemoglobin was resolved on Day 213 (PPD) and was considered not related to s.c HX575. The frequency of iron supplementation was increased from every month to every second week. No action was taken with s.c. HX575 and the patient continued in the study. Another patient underwent anti-epoetin antibody testing on Day 690 (PPD) after worsening of renal anemia. At this point, the patient had been on s.c. HX575 for at least 2 years. The patient had fluctuating hemoglobin and ferritin levels: hemoglobin at Visit 5: 5.2 g/dL, Visit 6: 7.6 g/dL, and Visit 7: 7.1 g/dL; ferritin levels at Visit 5, Visit 6, and Visit 7 were 46.7 ng/mL, 6.7 ng/mL and 32.0 ng/mL, respectively. Transferrin levels were not available. Since the ADA test result was negative, anti-epoetin antibody induced PRCA was ruled out. The frequency of iron supplementation was decreased from every week to as needed. No action was taken with s.c. HX575 and the patient continued in the study.
Discussion	This NI-PASS increased the dataset on the safe use of s.c. HX575 treatment of CKD-induced anemia under real-life post-approval conditions, with the primary objective of assessing and monitoring rare AESIs (particularly PRCA).

	Monitoring a safety analysis set (SAF) of 2497 patients and covering a total of 3600.2 patient years, the study detected no new safety signals; in particular no PRCA case occurred. The nature and frequencies of the reported AESIs and overall AEs are consistent with those of the known ADRs included in the SmPC. The current results indicated thromboembolic and cardiovascular events with an IR (per 1000 patient years) of 46 (95% CI: 39, 53), congestive heart failure with an IR of 33 (95% CI: 27, 39), and hypertension (worsening or newly developing hypertension, hypertensive crisis, uncontrolled hypertension) with an IR of 13 (95% CI: 10, 18). The study results reconfirmed that the s.c. administration route for HX575 treatment in renal anemia is well-tolerated with no new safety concerns noted in the study. The post-approval commitment that was agreed with European Medicines Agency (EMA) in March-2016 has therefore been fulfilled.
Marketing Authorization Holders	**European Union:** Sandoz GmbH Biochemiestrasse 10 6250 Kundl Austria Hexal AG Industriestrasse 25 83607 Holzkirchen Germany Medice Arzneimittel Pütter GmbH & Co KG Kuhloweg 37, 58638 Iserlohn Germany
Names and Affiliations of National Coordinating Investigators	Germany: PPD Italy: PPD Romania: PPD Slovakia: PPD Slovenia: PPD Spain: PPD There were no national coordinating investigators for Bulgaria, Croatia, Greece, and Poland

2 List of abbreviations

ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
BMI	Body Mass Index
CI	Confidence Interval
CKD	Chronic Kidney Disease
CRO	Contract Research Organization
CSR	Clinical Study Report
DBL	Database Lock
DMP	Data Management Plan
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EOS	End of study (defined as end of the individual observation period)
ESA	Erythropoietin/Erythropoiesis Stimulating Agent
FSAF	Full Safety Analysis Set
GFR	Glomerular Filtration Rate
HX575	Company code for epoetin alpha products Epoetin alfa Hexal® and Binocrit®
ICF	Informed Consent Form
INN	International Non-proprietary Name
IR	Incidence rate
iv	Intravenous
LLN	Lower Limit Normal
LOE	Lack of efficacy
MedDRA	Medical Dictionary for Regulatory Activities
NI-PASS	Non-interventional Post-Authorization Safety Study
PD	Protocol deviations
PI	Principal Investigator
PRCA	Pure Red Cell Aplasia
PT	Preferred Term
PV	Pharmacovigilance
RBC	Red Blood Cell
RMP	Risk Management Plan
SAE	Serious Adverse Event

SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
sc	Subcutaneous
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
std	Standard Deviation
TFL	Table, Listing, Figure
WBC	White Blood Cell
WHO	World Health Organization

3 Investigators

Contact details and a list of all investigators including national coordinating investigators, participating hospitals, and ECs for each site was kept in a stand-alone document, which is listed in Annex 1 and is available upon request.

4 Other responsible parties

Role/Responsibility	Name and Address of Organisation
Marketing Authorisation Holders contact person	PPD PPD Regulatory Affairs Sandoz Biopharmaceuticals Sandoz GmbH Biochemiestrasse 10 6250 Kundl Austria Phone: PPD Email: PPD
Clinical Research Organisation: Start-up/Regulatory set-up, Project Management/Site Monitoring, Data Management, Biostatistics, Medical Monitoring, Medical Writing	Pharm Research Associates (UK) Ltd. Cannon Place, 78 Cannon Street London, England, EC4N 6AF United Kingdom
EDC Vendor (subcontracted by Pharmaceutical Research Associates [UK] Ltd.)	EvidentIQ Germany Rosental 5 80331 Munich Germany
Logistical Laboratory Services for Hexal AG – Bioanalytics (Sample shipment)	Q2 Solutions 1201 South Collegeville Road Collegeville, PA 19426 USA
Central Laboratory Services (Anti-Drug Antibody)	Hexal AG – Clinical Bioanalytics Keltenring 1+3 D-82041 Oberhaching Germany

5 Milestones

Table 5-1 Study milestones

Milestone	Planned date	Actual date
First notification to a national competent authority (Italy)	NA	15-Dec-2016
Registration in the EU PAS register	December-2016	30-Dec-2016
First approval date of the Protocol by an IRB/EC (Germany)	31-Jan-2017	04-Jan-2017
Start of data collection	31-Mar-2017	12-Apr-2017
Last approval date of the Protocol by an IRB/EC (Italy)	30-Apr-2020	28-May-2020
End of data collection	07-Feb-2023	08-Feb-2023 (corresponding to data base lock)
Final report of study results	31-Oct-2023	19-Oct-2023 (content final)

6 Rationale and background

Endogenous erythropoietin is a glycoprotein hormone that is predominantly secreted by the peritubular interstitial cells of the kidneys in response to tissue hypoxia and stimulates red blood cell production in the bone marrow. All licensed epoetin alfa products share the same mechanism of action: binding to cell surface receptors for erythropoietin on erythroid progenitor cells activates a kinase-based response that results in bone marrow erythroid cell proliferation, differentiation and survival.

Erypo®/Eprex® (same product registered under two trade names in Europe), manufactured by Janssen-Cilag, was the first epoetin alfa that received regulatory approval in the EU in 1988.

Sandoz's epoetin alfa (company code: HX575) was authorized in the EU in 2007 as the first biosimilar epoetin alfa that was developed using Erypo®/Eprex® as reference drug, following the demonstration of similar quality, safety and efficacy profile.

Sandoz's epoetin alfa is marketed under 3 different brand names: Binocrit®, Epoetin alfa HEXAL® and Abseamed®. Marketing Authorization Holder of Abseamed® is Medice Arzneimittel Pütter GmbH & Co KG. The latter brand was out of scope of the HX575-507 study based on a company decision, however the study outcome data are also representative for Abseamed®. The company code HX575 was collectively used instead of the brand names Binocrit® and Epoetin alfa HEXAL® throughout the study protocol.

HX575 is currently authorized in all countries of the European Economic Area, in Switzerland, Australia, and in many other countries worldwide.

Since 31-Mar-2016, HX575 has additionally been authorized for the subcutaneous (s.c.) route of administration in patients with CKD-induced anemia (in addition to the i.v. mode of administration). To further increase confidence on the safe use of s.c. HX575 and to fulfill the post-approval commitment, this NI-PASS was conducted as the appropriate measure to identify

any risk associated with the s.c. administration route of HX575 in CKD patients under real-life post-approval conditions.

For further information related to the product characteristics of s.c. HX575, please refer to the Binocrit® SmPC or Epoetin alfa HEXAL® SmPC.

7 Research question and objectives

The purpose of this category 3 NI-PASS was to increase the dataset on the safe use of s.c. HX575 by extending the safety database of the product in patients with CKD-induced anemia, who received s.c. HX575 treatment and by monitoring closely the AE profile under real-life post-approval conditions. Approximately 2500 patients with CKD-induced anemia on s.c. HX575 therapy were planned to be enrolled. The planned duration of the observation period per patient was 24 months. This NI-PASS study concept was discussed and agreed upon with the EMA in March-2016 and is part of the EU Risk Management Plan.

This study adds further evidence for the safety and effectiveness of subcutaneously administered HX575 in CKD patients under real life conditions.

Primary objective

The primary objective of this study was to assess the incidence of relevant and expected rare AEs (defined as AESIs), in response to s.c. HX575 treatment in patients with CKD-induced anemia.

Secondary objectives

Secondary objectives of this NI-PASS study were to assess and to monitor the general safety, tolerability, and effectiveness of s.c. HX575 treatment in patients with CKD-induced anemia.

Study endpoints are summarized in Section 9.4.1.

8 Amendments and updates to the protocol

Data collection started on 10-Apr-2017 based on the original protocol (Version 1.0, dated 16-Sep-2016). There was one substantial protocol amendment. Amendment 1 (protocol Version 2.0, dated 23-Apr-2018) which is available upon request as per Annex 1 and which included changes mainly related to the clarification of study endpoints and study objectives ensuring focus on 'LOE' reporting, and defining additional details for data analysis. In addition, the variables in the study were re-structured, minor discrepancies were corrected, clarifications were added, organizational/personnel changes were implemented, study milestone dates were updated, and participation of additional countries was adopted. The details of Amendment 1 are described in Table 8-1.

This report describes the actual study conduct and statistical analysis as amended.

Table 8-1 Protocol amendment

Section of the study protocol	Amendment or update	Reason
Entire document	Study endpoints and study objectives	To further adjust and align the description of study objectives and endpoints throughout the document
Cover pages and Abstract	Title	Has been revised to reflect the adjusted study endpoints and study objectives
	Research question	Purpose of the study re-worded
	Country list	Scope of participating countries has been changed
	Authors' list and Market Authorization Holder contact person	Implemented personnel changes
	Study design	Uncontrolled changed to single arm because there is no control group in the study
	Introduction sentences of inclusion and exclusion criteria	Changed following updated template
	Variables	Re-structured and further information provided to make it more understandable and provide more clarity to sites on data collection
	Milestone dates	Updated according to progress of study
	List of Adverse Events of Special Interest (AESIs)	Updated based on product Summary of Product Characteristics (SmPC) and RMP
Abstract	Data sources	In some cases, part of electronic Case Report Form (eCRF) data might be used as data source documents
Section 2	List of abbreviations	New terms were inserted, not used terms were deleted to adapt list to the needs of the amendment
Section 6	Milestone dates	Updated according to progress of study
Section 7	HX575 company code usage in the document	Clarification provided to explain that HX575 was collectively used instead of Binocrit® and Epoetin alfa HEXAL® brand names throughout the study protocol
	Manufacturer of Erypo®/Eprex®	Corrected – Marketing Authorization Holder of reference product was Janssen-Cilag
	New indication of reference product	Marketing authorization of Erypo®/Eprex® was extended to a new indication
Section 8	Research question	Purpose of the study re-worded
Section 9	eCRF data entry	eCRF data entry was allowed for designated site staff members, not limited to physicians only
	Data sources	In some cases, part of eCRF data might be used as data source documents
Section 9.2	Patient eligibility	Clarification provided on patient eligibility
	Introduction sentences of inclusion and exclusion criteria	Changed to adapt Hexal AG's template

Section of the study protocol	Amendment or update	Reason
Section 9.3	Variables	Re-structured and further information provided to make it more understandable and provide more clarity to sites on data collected
Section 9.4	Data collection schedule	New paragraphs inserted to provide clarification on data collection and data collection time points
Table 9-1	Assessments	Clarification provided because some assessments could not be waived
	Visit windows	Visit windows were deleted, clarification provided for data collection time points
Section 9.7	Data analysis	Further details of data analysis provided
Section 11	Local Person Pharmacovigilance and Central Case Processing Site terminologies	Replaced by new terminologies due to Standard Operating Procedure (SOP) and process changes; new terms: local Pharmacovigilance (PV) department and Novartis Chief Medical Office and Patient Safety
	Contact information of local PV department	Emphasized location of contact details at several times throughout the safety section to ensure information was not missed
	Pregnancies	Data collection on male study patients' partner pregnancy removed
Section 11.1	List of special case Scenarios	Amended based on new applicable SOPs and the character/needs of the study
Section 11.2	Transmission of infectious disease via medication	Removed as individual bullet point from SAE definition and added further clarification about its reporting based on new applicable SOPs
	Reporting of positive anti-epoetin antibody results to local PV department	Deleted due to process revision
	List of AESIs	Updated based on product SmPC and Risk Management Plan
Section 13	References	Binocrit® SmPC information updated and Epoetin alfa HEXAL® SmPC added; new reference provided for pure red cell aplasia

9 Research methods

9.1 Study design

This was an observational (i.e. non-interventional), multi-center, open-label, single arm NI-PASS in patients treated for CKD-induced anemia, with or without dialysis. In this study, commercially available s.c. HX575 (limited to Binocrit®/Epoetin alfa HEXAL®) was used as prescribed per the treating physician's best clinical judgment for CKD-induced anemia.

Abseamed® was out of scope of the HX575-507 study as per the protocol and a company decision. However, the data collected for Binocrit® and Epoetin alfa HEXAL® are representative for Abseamed® as well.

The decision to treat the patient with s.c. HX575 was independent from the decision to include the patient into this NI-PASS. Since this was an observational study, only data available from routine clinical practice and standard of care in line with national and international laws and regulations were recorded. This NI-PASS did not impose any mandatory treatment regimens nor required specific assessments or tests by the treating physician.

Patients were eligible for inclusion in this study if they fulfilled all inclusion criteria but none of the exclusion criteria defined in the protocol. Eligible patients who consented to participate in the study entered the observation period of planned 24 months. HX575 was to be administered through the s.c. route only and, with respect to doses and dosing schemes, in accordance with the current Binocrit®/Epoetin alfa HEXAL® SmPC, but the actual dosing regimen was at the treating physician's discretion. During the study, certain medical data were collected, related to the CKD disease status, the use of s.c. HX575, and its safety and effectiveness. During the observation period patients were allowed to take other medications as deemed appropriate by the treating physician; the medications might have been changed during the observation period in line with the observational nature of the study. Data were to be documented at specified data collection time points, i.e. at the time of enrollment into the study (Visit 1, V1), after 4 -, 8-, 12-, 16- and 20-months (V2-V6) and at the end of the individual observation period (EOS) after 24 months or premature discontinuation.

Data for the study were transcribed and entered by the treating physician or his/her designee into an eCRF from the patient's medical records. In some cases, when certain information was not recorded in the source documents (e.g. inclusion/exclusion criteria, medical history start/end dates, primary mechanism of chronic kidney disease etc.) as per the study site's usual clinical practices, part of the eCRF served as source documentation. In these cases, a document had to be available at the study site clearly identifying those data fields that were recorded directly in the eCRF, and for which the eCRF was to stand as the source document.

9.2 Setting

It was planned to enrol in this study approximately 2500 patients with CKD-induced anemia on s.c. HX575 therapy in approximately 250 sites and approximately 9 European countries.

Finally, the study was conducted in 129 sites in the following 10 European countries: Bulgaria, Croatia, Germany, Greece, Italy, Poland, Romania, Slovakia, Slovenia, and Spain and enrolled 2510 eligible patients.

A list of treating physicians and study sites can be provided upon request (see Annex 1).

The sites in this study included hospitals and individual medical practices which provided only data available from routine clinical practice and standard of care in line with national and international laws and regulations.

Eligible patients entered the planned observation period of about 24 months but there were slightly more than half of the patients (see Table 10-1) who were documented for more and slightly less than half of the patients who were documented less than 24 months. Prematurely discontinued patients were not replaced.

The actual enrolment for this study took place from 10-Apr-2017 (enrolment of first patient) to 06-Nov-2020 (enrolment of last patient). Data were collected from 12-Apr-2017 (Start of data

collection) to 08-Feb-2023 (End of data collection corresponding to data base lock, after the conclusion of data cleaning activities).

9.3 Subjects

Patients of both genders with CKD-induced anemia with or without dialysis treatment who were on chronic s.c. HX575 treatment or who just recently commenced HX575 s.c. treatment (i.e. who had started s.c. HX575 at least one day prior to provision of informed consent) were eligible for this study provided they also fulfilled all inclusion criteria but none of the exclusion criteria at the time of informed consent provision.

Both common types of dialysis were acceptable for this study (hemodialysis and peritoneal dialysis) if the medical care was provided by a certified nephrology/dialysis center. It was planned to enroll patients on s.c. HX575 treatment who were followed-up for a period of 24 months of treatment or until discontinuation of s.c. HX575 treatment, or switched to the i.v. route administration, or switched to a different ESA, whichever occurred first.

Eligible patients were to be enrolled into the study earliest 1 day after initiation of s.c. HX575 treatment.

The patients had to provide written informed consent to allow the use and/or disclosure of patient's personal and/or health data in a pseudonymized manner before entry into the study. It was important that the patient personally signed and dated two written copies of ICF prior to enrollment after having received written and verbal information about this NI-PASS from the treating physician. One original copy was kept by the treating physician and the patient received the second original copy.

All versions of the English Master Sample of the written information and ICF can be provided upon request (Annex 1).

Data of patients were to be excluded if no evidence of a signed ICF was available (see Section 10.1.1).

Inclusion criteria

Patients eligible for inclusion in this study fulfilled **all** of the following criteria:

- Diagnosis of CKD-induced anemia with or without dialysis treatment
- Age ≥ 18 years
- Treatment with s.c. HX575 for at least 1 day prior to informed consent
- Provision of written informed consent

Exclusion criteria

Patients who fulfilled **any** of the following criteria were **not** eligible for inclusion in this study:

- Known primary LOE to a recombinant ESA product
- History of treatment with an erythropoietin/ESA product which was not authorized in the EU
- History of PRCA or any other type of aplastic anemia
- History of anti-epoetin antibodies
- Uncontrolled hypertension

- Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1. of the Binocrit®/Epoetin alfa HEXAL® SmPC
- Patients scheduled for surgery who, for any reason, could not receive adequate antithrombotic prophylaxis
- Currently participated in an interventional clinical trial (at the time of study entry)
- Pregnancy (confirmed or suspected) or breastfeeding woman

9.4 Variables

9.4.1 Endpoints

Primary endpoint

The primary endpoints were the incidence of the following AESIs:

- PRCA
- LOE
- Major thromboembolic and cardiovascular events
- Congestive heart failure
- Hypertension (worsening or newly developing hypertension, hypertensive crisis, uncontrolled hypertension)
- Seizures
- Posterior reversible encephalopathy syndrome
- Blood disorders (white blood cell lineage disorders, thrombocythemia and porphyria)
- De-novo malignancies, unexpected tumor growth
- Hypersensitivity reactions, anaphylaxis including. serious skin reactions
- Hyperkalemia

Secondary endpoints

The following secondary endpoints were to be assessed:

- Incidence of SAEs
- Incidence of AEs
- Number of patients discontinuing the study prematurely and reasons for discontinuations
- Red blood hematology parameters over time: hemoglobin concentration, RBC, absolute and relative reticulocyte counts, hematocrit
- Number of patients who received transfusions (whole blood and/or packed RBC)
- Weekly epoetin dosage over time

Other endpoints

The following other endpoints specified in the SAP were to be assessed:

- Other hematology parameters over time: platelets, WBC, neutrophils, lymphocytes, monocytes, eosinophils and basophils
- Iron status over time: ferritin, transferrin saturation
- Iron supplementation

9.4.2 Data variables collected

This was a non-interventional study and did not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule. The variables in the following data collection schedule (Table 9-1) were to be collected but only, if routinely assessed during clinical practice and standard of care and if documented in the patient's medical records:

Table 9-1 Data collection schedule

Data collection time point **Assessments, if performed as part of routine clinical practice/standard of care**	***V1*** **Baseline assessment and start of observation period**	***V2-V6[4]*** **Data Collection Time Points every 4 months**	***EOS*** **End of observation period 24 months after start of observation period or premature discontinuation of s.c. HX575 treatment**
Written informed consent[1, 5]	X	NA	
Verification of suitability criteria for participation[5]	X		
Demographic data	X		
Medical history, concomitant diseases and medications	X		
Iron status	X	X	X
Dialysis modalities	X	X	X
Body weight (post-dialysis)	X	X	X
Hematology laboratory values	X	X	X
Start of s.c. HX575 treatment documentation	X		
Changes in s.c. HX575 treatment[2]	NA	X	X
Changes in concomitant medication[2]	NA	X	X
Changes in concomitant disease[2]	NA	X	X
Transfusion information	NA	X	X
Study discontinuation (date and reason) [5]	NA		X
AEs and AEs of Special Interest[3, 5]	X	continuous documentation as applicable	
Optional serum sample(s) for the assessment of anti-epoetin antibodies in case of suspected LOE or PRCA			

[1] s.c. HX575 treatment had to start at least 1 day prior to signature of informed consent;

[2] Only the change compared to the previous visit was to be documented;

[3] For AEs of Special Interest refer to Section 9.4.1;

[4] Additional unscheduled data collection time points were necessary in case of serious adverse drug reactions and/or LOE or PRCA;

[5] Assessment could not be waived. Some unresponsive sites were administratively closed so the date and reason for discontinuation were not documented.

Demographics

Age, gender and height were to be assessed at the first data collection time point. Body weight (post-dialysis) was to be collected at every scheduled data collection time point (4 monthly).

Relevant medical history

The relevant medical history was to be collected. Of relevance was all information related to the following:

- CKD (mechanism, onset date, stage)
- Renal anemia (onset date, severity)
- Serious infections which required hospitalization (admission and discharge dates) during the last 12 months prior to informed consent
- Other relevant medical history e.g. allergies, hypersensitivities and intolerabilities; cardiovascular disorders, previous thromboembolic events and cerebrovascular accidents; underlying diagnosis(es) which caused CKD and secondary diagnoses which resulted from CKD (term, start and end dates or ongoing)

Concomitant medications

The following information about concomitant treatment were to be collected:

- Previous use of ESA (start and end date or ongoing, mode of administration, INN, trade name)
- s.c. HX575 treatment (trade name, start and end date or ongoing, dose, mode of administration, frequency, dose adaptation/changes as compared to the previous visit, treatment interruptions)
- Other concomitant medication/therapies (INN, start and end date or ongoing)

Hematology parameters

The following hematology parameters were to be collected:

- Serum hemoglobin, erythrocytes, reticulocytes (absolute count and relative count in %), hematocrit, platelets, white blood cells including. differentiation (collection date, result, normal range, clinical significance)

Dialysis modalities

Dialysis modalities were to be collected at every data collection time point:

- Actual GFR/eGFR, type of dialysis, start date, change of dialysis type

Iron status/supplementation

The following iron status and iron supplementation data were to be collected:

- Iron status (test date, serum ferritin result, clinical significance, and percentage of transferrin saturated with iron result)
- Iron supplementation (brand name, formulation, dose, frequency, mode of administration).

Transfusions

Transfusion data were to be collected at every data collection time point:

- Type of transfusion, reasons for transfusion, date and volume of transfusion

Adverse events

Adverse events (verbatim, evaluation of fulfillment of criteria for AESI, start and end date, outcome, intensity, action taken, relationship to study drug, and seriousness) were to be

collected. The AESIs were defined due to inconsistencies in the data entered by the investigators in the "Is this AE considered a per protocol event of special interest" field on the Adverse Event CRF, the CRF field were not to be used for analysis and the categories listed above were to be mapped exclusively based on SOC and PTs as provided by study medical team.

Adverse events that started on or after informed consent date and up to and including 30 days after the end of study date are presented for the analysis. Any adverse events starting after 30 days after the end of study date were not part of the tabulations and were reported separately in Listing 2.6.

However, those reported AEs that started after 30 days after individual end of study date (50 AEs in 38 patients) are part of the Sandoz safety database. They did not reflect any new safety signals and were reported in compliance with the routine pharmacovigilance reporting, if applicable.

Any SAEs experienced after 30 days after the patient has stopped study participation should have been only reported to the Sponsor if the treating physician or other involved health care professional suspected a causal relationship to the drug of interest.

Due to the already large safety data base of s.c. HX575 and due to the fact that certain AEs occurred related to the procedures of dialysis and s.c. injection, the following AE reporting exemptions were provided as per protocol in order to allow a more targeted AE reporting approach for relevant events:

- Shunt/arteriovenous fistula complications:

Any AE related to shunt/arteriovenous fistula complications were to be considered a reportable AE only if the event was considered a significant complication requiring a specific medical and/or surgical intervention.

- Laboratory values out of normal ranges:

Laboratory values out of normal ranges were to be considered a reportable AE only if they were clinically significant, i.e. were to be related to:

- Clinical sign and symptoms that were considered (S)AEs, and/or
- Required a specific therapy or medical procedures (e.g. phlebotomy) and/or
- Were the reason for a change in the routine medical treatment for this patient.
- Injection site reactions:

Injection site reactions were to be considered a reportable AE only if they exceeded the reasonably expected level of discomfort and/or clinical signs and symptoms of an s.c. injection according to the judgement of the treating physician, or if the seriousness criteria for the event were met.

- Expected AEs during or directly after dialysis and not suspected to be related to HX575:

Expected and frequently occurring AEs during or directly after dialysis such as dizziness, vertigo, weakness, nausea, headache, cough, fatigue, hypertension, hypotension, etc., were to be considered a reportable AE only if clinically relevant (i.e. requiring a specific medical intervention and/or treatment), if the seriousness criteria for the event were met and/or a causal relationship to s.c. HX575 was suspected by the treating physician.

Diagnosis of PRCA

If the reticulocyte count was low (< 20,000/mm^3 or < 20×10^9/L), platelet and white blood cell counts were normal, and if no other cause of LOE was suspected, anti-epoetin antibodies were to be assessed in the serum and a bone marrow examination was to be considered for the diagnosis of a PRCA at the clinical site or at a specific site for hematology diagnostics (Boven et al 2005).

If a diagnosis of anti-epoetin antibodies-mediated PRCA was suspected, therapy with s.c. HX575 had to be discontinued immediately. No other epoetin/ESA therapy was to be commenced because of the risk of cross-reaction. Appropriate therapy, as per the local practice for treatment of PRCA, was to be initiated at the institution/participating site where the patient was treated.

Anti-epoetin antibodies assessment in case of LOE with suspected PRCA

When determination of anti-epoetin antibodies was considered clinically warranted by the treating physician, this could have been performed in the local laboratory. In addition, Hexal AG offered the possibility of sending patient serum (that had been taken in accordance with clinical routine practice and standard of care) to the bioanalytical laboratory of Hexal AG, Oberhaching, Germany, for a highly sensitive assessment of presence of the anti-epoetin antibodies (and, in case of a confirmed positive-binding ADA result, subsequent testing for anti-epoetin neutralizing antibodies). The ADA testing results were to be communicated to the treating physician as soon as available. In order to harmonize and facilitate blood sampling and sample shipment for the anti-epoetin antibodies assessment, the treating physician received a handling manual with detailed information and instructions including the address of central laboratory.

According to the Binocrit®/Epoetin alfa HEXAL® SmPC, LOE is defined by a decrease in hemoglobin (1 to 2 g/dL or 0.62 to 1.25 mmol/L per month) with increased need for transfusions in patients who previously responded to Binocrit®/Epoetin alfa HEXAL® therapy. Consequently, subsequent diagnostic procedures comprised of (at least) a reticulocyte count and exclusion of other typical causes of non-response (e.g. iron, folate or vitamin B_{12} deficiency, aluminum intoxication, infection or inflammation, blood loss, hemolysis and bone marrow fibrosis of any origin).

A paradoxical decrease in hemoglobin and development of severe anemia associated with low reticulocyte counts had to lead to immediate discontinuation of the treatment with s.c. HX575 and performing of anti-epoetin antibody testing to investigate the possibility of an occurrence of PRCA.

The following information about anti-epoetin antibody assessments were to be collected:

- Assay details, ADA assay result, titer, neutralizing antibody assay result, serum sample collection and shipment date, specimen number

End of study data

The following study data were to be collected for each individual patient at the end-of-study (i.e. last) visit:

- Completion of study (“YES” or “NO”)

- Completion date
- Last administration date of s.c. HX575
- Reason for not completing study for one of the following categories (if applicable): AE(s), treatment contraindicated as per SmPC, unsatisfactory therapeutic effect (other than LOE), LOE, switch to other ESA treatment, switch from s.c. to i.v. treatment, patient's condition no longer required study treatment, patient withdrew consent, lost to follow-up, related to health insurance/reimbursement, death or other (see Section 10.1.2 for a summary of the reasons for early study discontinuation).

9.5 Data sources and measurement

Data sources for data collection were the patient's medical record available at the clinical site. In some cases, when certain information was not recorded in the source documents (e.g. inclusion/exclusion criteria, medical history start/end dates, primary mechanism of chronic kidney disease etc.) as per the study site's usual clinical practices, part of the eCRF served as source documentation. In these cases, a document was available at the study site which clearly identified those data fields that were recorded directly in the eCRF, and for which the eCRF stood as the source document.

The sites that enrolled patients in this NI-PASS recorded the data in a pseudonymized manner in an eCRF provided by the CRO, which captured, checked, stored and analyzed the data. The eCRFs were reviewed for any inconsistencies and when necessary, queries were raised. Data collected were verified against the source data to an extent described in the Monitoring Plan for the study.

A fully validated EDC system was used. All entries/adjustments into the EDC system had to be performed by the site; self-evident corrections within the eCRF were not allowed. Automated checks were programmed identifying discrepancies during data capture; in addition, medical and data review were performed as outlined in the DMP. The treating physician electronically signed off the eCRF pages and to confirm that the entered data were complete and accurate.

After DBL, the treating physician received completed eCRFs as compact discs via a secure mode of transfer for archiving at the investigational site.

Further details of the handling of the study data were outlined in the DMP and/or its respective appendices.

Concomitant or prior medications entered into the database were coded using the WHO Drug Reference List. Medical history/current medical conditions and AEs were coded using MedDRA terminology.

Safety and clinical data were transferred to the Hexal AG at a frequency defined in the CRO contract and per the respective data transfer specifications.

Patients were to be treated according to the local prescribing information, and routine medical practice and standard of care in terms of visit frequency and types of assessments performed and only these data were collected as part of the study.

Throughout the individual observational period of planned 24 months, the treating physician or his/her designee was asked to document patient data in the eCRF at pre-defined data collection

time points. All data collection time points were independent of the patient visits at the clinical site and patients had to stick to their routine visit schedule.

ICF signature date was considered as start of the individual observational period and starting point of AE reporting. Data collection time point (V1) was expected to occur on the same date as the ICF signature but not earlier than ICF signature.

At V1, the physician or his/her designee was asked to document the data of the regular patient visit at the clinical site at the date of ICF signature. If no relevant data were available from this visit, the earliest patient visit at the clinical site after ICF signature was documented. At V1, relevant medical history was documented retrospectively.

Subsequent regular data collection time points (V2-V6; EOS) followed every 4 months until completion of the individual observational period, which could have been before (premature patient discontinuation) or at 24 months (as planned) or thereafter (recorded as a PD).

All target dates of the regular four monthly data collection time points were related to the actual date of the ICF signature.

At each regular data collection time point, the site recorded patient's data up to the last available physical visit at the study site prior to the data collection time point. If no new physical patient visit at the clinical site occurred between the last recorded data collection time point and the current data collection time point, the current data collection time point was not completed and data entry continued at the next scheduled data collection time point.

Additional unscheduled data collection time points were completed in the eCRF in case of Serious Adverse Drug Reactions and/or LOE or PRCA.

AEs were documented in the eCRF on an ongoing basis starting at ICF signature.

The data collection schedule (see Table 9-1) that was designed and elaborated in alignment with the general and internationally accepted patterns of routine clinical practice and standard of care of patients with CKD-induced anemia being treated with s.c. HX575 or any other erythropoietin/ESA.

9.6 Bias

This was an open-label single arm study.

Primarily, this NI-PASS intended to collect safety and immunogenicity data for the s.c. route of administration of HX575 over a 24-month treatment period in the most sensitive, immunocompetent population (patients with CKD).

The study utilized convenience sampling and selection bias might not be fully excluded. While limited to centers using s.c. HX575, attempts were made to enroll a variety of centers from each country with regard to center size and academic affiliation (e.g. academic as well as academic-affiliated and non-academic).

In this open-label study, only patients treated with s.c. HX575 were included and there were no comparison groups of either untreated patients or patients treated with other ESAs. Due to the non-interventional nature of this NI-PASS it might be that some data points were missing due to adaptations or changes of the medical practice or other reasons.

9.7 Study size

Approximately 2500 patients with CKD-induced anemia on s.c. HX575 therapy were planned to be enrolled. The planned duration of the observation period per patient was 24 months.

9.8 Data transformation

The SAP version 3.0 (dated on 31-Jan-2023 was finalized before DBL) includes details regarding data transformation procedures performed for statistical analysis of the study. Section 9.9 includes all items related to statistical methods.

9.9 Statistical methods

All analyses were conducted as described in the SAP. The SAP (version 3.0) is available upon request as per Annex 1.

Statistical analyses were performed using SAS® version 9.4 or higher. Appropriate SAS programs were prepared and validated according to the CRO's SOPs.

AEs and medical history were coded using MedDRA, version 25.1 or higher. Previous and concomitant medications were coded using the PRAWHODRUG2022SEP01GLOBAL_B3.

9.9.1 Main summary measures

As this was a single arm study, only descriptive statistical methods were applied. The following descriptive statistics were shown in summary tables

- Continuous variables: n (non-missing cases), mean, median, std, 1st quartile (Q1), 3rd quartile (Q3), minimum, maximum, nmiss (number of missing cases, e.g. for each visit).
- Categorical variables: Count and percentage of category. Percentages are based on the total category count excluding the missing category if not otherwise mentioned.

Analysis by visit showed data collection time points 1 to 7 unless otherwise specified.

For summaries of AEs, incidences in terms of frequencies were presented with exact 95% Clopper-Pearson CI. In addition, IRs were calculated relative to patient years duration at risk and presented together with 2-sided 95% CI.

Further details including potential exploratory analyses are provided in the SAP.

9.9.2 Main statistical methods

Statistical analyses were based on standard descriptive methods.

The incidence of AESI (i.e., primary study endpoint) were presented together with exact 2-sided 95% Clopper-Pearson CI. In addition, IRs were calculated relative to patient years (i.e., per 1000 patient years) duration at risk and presented together with 2-sided 95% CI.

The following calculations were followed as per the SAP:

- Time since event was calculated in years as: Time since event (years)=(Date of informed consent–Date of event)/365.25
- Duration (duration at risk) was calculated in years as: Duration (years)=(Date of event–Date of informed consent+ 1)/365.25.

Note: 'Event' refers to the occurrence of e.g, 'Diagnosis of CKD/renal anemia', start of current/initial dialysis', 'first ESA treatment', as described in the SAP. Only when calculating Patient years an event refers to an AE.

- BMI was calculated as: BMI (kg/m^2)=Body Weight (kg)/(Height [m])^2
- Duration since first subcutaneous HX575 treatment was calculated as: Duration (years)=(Date of last study drug–date of first subcutaneous HX575 treatment+ 1)/365.25

For any analyses presented in months, one month was defined as 30.5 days.

Definitions of analysis sets

All enrolled patients: included all patients who signed the informed consent and fulfilled all inclusion criteria but none of the exclusion criteria at the time of informed consent provision.

Safety analysis set: consists of all enrolled patients who had at least 1 study assessment.

Due to unresponsive sites where it was not possible to obtain physician signatures for all patients, the following rules apply:

- If the patient's Inclusion/Exclusion criteria CRF was not signed, then the patient would be excluded from the Enrolled Set and the Safety Set.
- If the patient had the Inclusion/Exclusion criteria CRF signed but the Binocrit Epoetin alfa HEXAL AG Treatment CRF was not signed, then the patient would be excluded from the Safety Set only.

These exclusions were determined via a manual review of patients with unsigned CRFs and all decisions were documented prior to DBL in a data review meeting.

FSAF: consists of all enrolled patients who have at least one study assessment regardless of physician signatures being obtained at DBL.

9.9.3 Methods used to examine subgroups and interactions

Not applicable.

9.9.4 Missing values

Partial dates prior to the study

For the date of the event at least the year had to be present for a duration to be calculated. If a day of the event was missing it was substituted by 15. If day and month of event were missing they were substituted by 01-July. If an imputed date was after the informed consent date, informed consent date was used instead.

In listings original (not-imputed) dates were presented.

Partial dates during the study

If the study discontinuation date or the start of AE date or dialysis start date was partial, the day was substituted either by 01 (month by January) or the day (month) of the last visit date prior to discontinuation or AE, whichever was later.

For the calculation of overall and average weekly s.c. HX575 doses: the partial start dates were imputed with a missing day substituted by 01 (month by January); partial end dates were imputed with the latest possible date (month by December, day by last day in the month), unless it became after the start date of the next interval, in which case (and also in case of completely missing date) it was set to the start date of the next interval minus 1. Missing dates for the last interval were set to the date of last study drug taken from completion/discontinuation page.

In listings original (not-imputed) dates were presented.

9.9.5 Sensitivity analyses

In case a considerable amount (more than 10%) of partial dates were available for the duration of risk despite expectations, a sensitivity analysis was planned to be performed substituting the start of the AE by a different date, e.g. by 15 (01-July) or the middle of the two visits before and after. As the criteria was not met, this sensitivity analysis was not performed.

A reduced number of AEs (i.e., <1%) were not reported directly in the EDC (the primary source) and only captured in a safety database (the secondary source). A list of AEs captured in the safety database were incorporated in the analysis. A sensitivity analysis was performed using data from both sources to derive the incidence and IRs and was included as a separate overall AE tabulation. This set of AEs documented in the safety database are reported in a separate listing (Listing 2.5.1). During the final data review meeting some patients with unsigned CRFs were identified. Therefore, Hexal AG and CRO teams decided to include a further analysis set (i.e., FSAF) to account for AEs that were captured in EDC by those patients.

A separate overview AE summary table was included for the FSAF. Additionally, a new listing was provided with any AEs not reported in the main analysis but included in the FSAF (Listing 2.5.2).

9.9.6 Amendments to the statistical analysis plan

The SAP includes a section “Document History” with details of the changes performed to the SAP after first approval (v1.0 by 19-Jun-2018) after any dry run and/or interim analyses performed in the study. None of the interim analyses resulted in Interim Reports. Changes to the SAP were made to more clearly present the results in TFLs, add more details to TFLs and/or to clarify any derivation needed for the analyses. The SAP was finalized before DBL.

9.9.7 Re-analysis of data after database lock

After DBL it was identified that erroneous data was entered for 1 patient who was confirmed by the site investigator to not exist. A decision was taken by the sponsor to programmatically excluded this patient from the final analysis. This process was documented in the hard-coding plan.

Following the implementation of the hard-coding, the final analysis datasets and TFLs were rerun.

9.10 Quality control

Data quality and integrity, including accuracy and legibility of collected data and original documents, were controlled by the following measures:

Data quality management

A designated CRO assured database quality by reviewing the data entered into the eCRFs by the site staff for completeness and accuracy, and in accordance with the data validation plan.

Data recording and document retention

The treating physician maintained the source documents for each patient in the study, which consisted of case and visit notes (hospital or clinic medical records) containing demographic and medical information, and the results of any other tests or assessments. In general information entered in the eCRF had to be traceable to these source documents in the patient's file. In some cases, when certain information was not recorded in the source documents as per the study site's usual clinical practices, part of the eCRF served as source documentation. In these cases, a document was available at the study site clearly identifying those data fields that were recorded directly in the eCRF, and for which the eCRF stood as the source document.

The treating physician kept the original ICF signed by the patient (a signed copy was given to the patient). The physician gave Hexal AG (or designee) access to all relevant source documents to confirm their consistency with the eCRF entries. No information from source documents about the identity of the patients was disclosed.

All documentation and data collected for the study are archived for at least 15 years after study termination or longer if required by national and local legal requirements. The documents are to be only destroyed after obtaining a written agreement from Hexal AG.

Site monitoring

Formal site monitoring was performed by the designated CRO as described in the monitoring plan for this study. Hexal AG assured compliance with the monitoring requirements.

Monitoring activity included reviews of the progress of the study and compliance with the protocol, standard operating procedures and applicable guidelines.

COVID-19 pandemic onsite visits were postponed due to local constricts and site monitoring calls were also cancelled due to the increased workload of the site staff. COVID-19 pandemic outbreak led to cancellation or postponement of patients' routinely scheduled visits. This was particularly observed for patients not being on dialysis treatment during their observation period.

Patients who were discontinued from the study due to COVID-19 pandemic are described in Section 10.1.2 and patients who discontinued from the study due to AEs of COVID-19 are described in Section 10.6.7.

10 Results

The data collected in this study were analyzed by means of descriptive summary statistics.

Summary tables and figures were prepared for all enrolled patients, SAF, and FSAF. The main results are presented in this report.

All tables, figures, and listings are provided in Annex 1 and are available upon request.

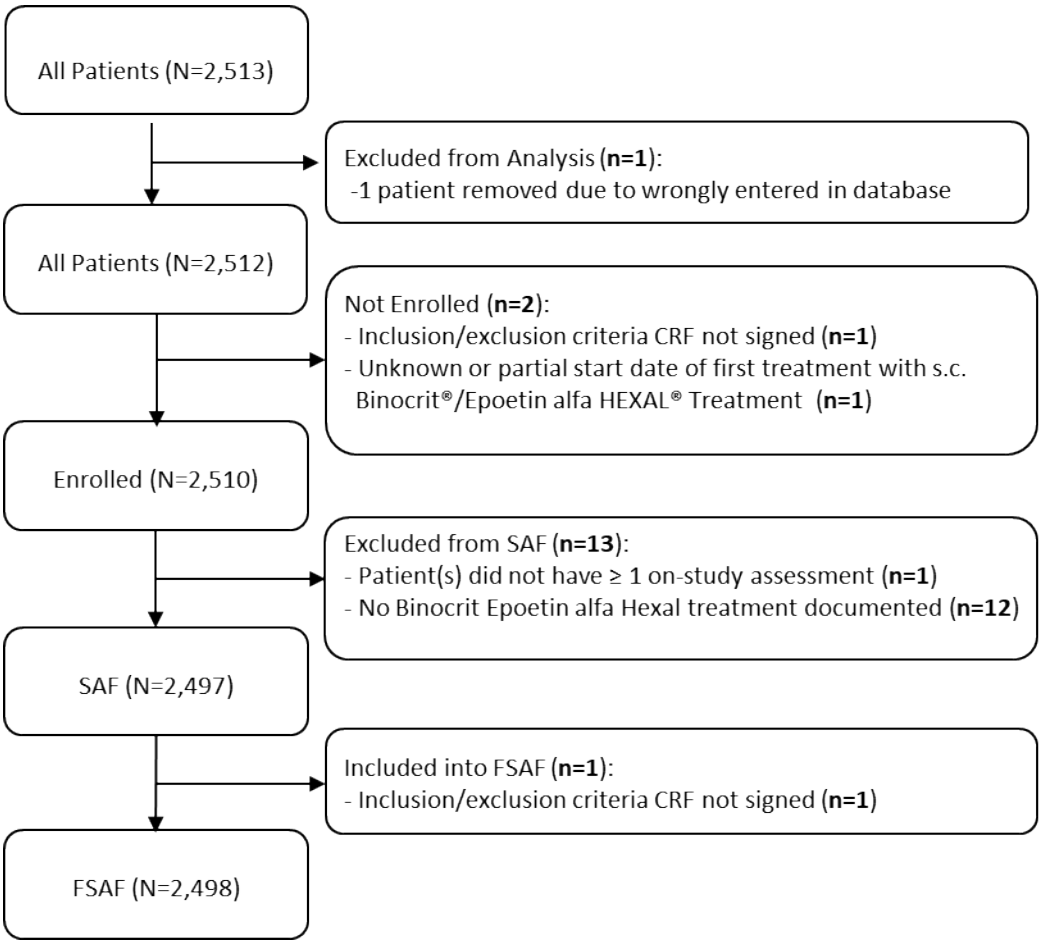
10.1 Participants

The patient analysis set are summarized in Figure 10-1. The disposition of patients is provided in Table 10-1.

The main analyses were conducted on the SAF, which included 2497 patients. Thirteen enrolled patients were excluded from safety analysis because they did not have a single documented study assessment (1 patient) or did not receive s.c. HX575 (12 patients).

10.1.1 Analysis sets

Figure 10-1 Patient analysis sets



All patients: All patients included in the electronic data capture system and who were screened for study eligibility

Enrolled: All enrolled patients who signed the informed consent form and fulfilled all inclusion/exclusion criteria

SAF: All enrolled patients who had at least one study assessment

FSAF: All enrolled patients who have at least one study assessment regardless of physician signatures being obtained at DBL

Source: Table 1.1.2

10.1.2 Patient disposition

Patient disposition and the reasons for premature study discontinuation including the other reasons are summarized in Table 10-1.

Of the 2510 eligible patients enrolled in the study: 2497 patients (99.5%) were included in the SAF, of which 1334 patients (53.1%) completed the study, and 1176 patients (46.9%) prematurely discontinued the study as per investigator decision.

The most common reasons for discontinuation of patients from the study were death in 476 patients (40.5%) and lost to follow-up in 170 patients (14.5%).

There were 4 patients who discontinued the study due to COVID-19 pandemic. The reasons were: patient afraid to visit hospital due to COVID-19 (2 patients), site transformed to COVID-19 unit and patient moved to different nephrology unit (1 patient), and COVID-19 restrictions (1 patient).

Table 10-1 Patient disposition (All enrolled patients)

Variable	Binocrit/Epoetin alfa HEXAL (N=2510)
Enrolled	2510
Safety analysis set[a] [n (%)]	2497 (99.5)
Completed study[a] [n (%)]	1334 (53.1)
Discontinued study[a] [n (%)]	1176 (46.9)
Reasons for study discontinuation[b] [n (%)]	
Death	476 (40.5)
Lost to follow-up	170 (14.5)
Patient enrolled at a site administratively closed with <732 days on study	130 (11.1)
Other	124 (10.5)
Transplantation	33 (2.8)
Changed nephrology site	31 (2.6)
Patient decision	13 (1.1)
Start of hemodialysis	12 (1.0)
Switch to other ESA	10 (0.9)
Switch to other treatment scheme	8 (0.7)
Patient's condition	5 (0.4)
Medical decision	4 (0.3)
PI ended up participating in the study	4 (0.3)

Variable	Binocrit/Epoetin alfa HEXAL (N=2510)
Treatment changed by non-study physician	2 (0.2)
Lost to follow-up	1 (0.1)
Non-compliance of the patient	1 (0.1)
Switch from s.c. to i.v. treatment	104 (8.8)
Patient´s condition no longer requires study treatment	85 (7.2)
Switch to long acting ESA treatment	33 (2.8)
Patient withdrew consent	31 (2.6)
Adverse event	20 (1.7)
Related to health insurance/reimbursement	2 (0.2)
Unsatisfactory therapeutic effect (other than lack of efficacy)	1 (0.1)
Lack of efficacy	0
Unknown	0
Study duration (years)	
n	2510
Mean (std)	1.47 (0.641)
Median	1.83
Q1, Q3	0.94, 1.98
Min, Max	<0.1, 2.6
Patient years in the study	3683.5

a. Percentages based on the number of patients enrolled.
b. Percentages are based on the number of patients that discontinued the study.
Note: If the end of study eCRF information is not available at database lock: if the patient completed ≥732 days on study then the patient is counted under completed study; if the patient had <732 days on study then the patient is counted under discontinued study: if the patient is from an administratively closed site then the reason for discontinuation is reported as “Patient enrolled at a site administratively closed with <732 days on study”; if the patient is not from an administratively closed site then the reason for discontinuation is reported as “Unknown”. The number of sites administratively closed with patients enrolled <732 days on study is 16, used for analysis.
Study duration is calculated as (end of study date - informed consent date + 1)/365.25.
Source: Table 1.1.2 and Listing 1.1.

Recruitment and study completion by country

Recruitment by country, enrolled patients, discontinued patients, completers and those observed in the study >24 months are provided in Table 10-2.

The majority of patients were recruited at sites in Germany, Italy, Bulgaria, or Greece.

The duration of observation was longer than the planned duration of 24 months for 92 (3.7%) of the enrolled patients. The instances of patient observation for more than 24 months were reported as protocol deviations (Section 10.2.2).

Table 10-2 Recruitment by country and site (All enrolled patients)

Country (# sites)	All enrolled patients (N=2510)	Safety analysis set (N=2497)	Discontinued patients (N=1176)	Completed patients (N=1334)	Patients who completed > 24 Months (N=92)
Germany (28 sites)	751 (29.9)	748 (30.0)	323 (27.5)	428 (32.1)	9 (9.8)
Italy (42 sites)	489 (19.5)	480 (19.2)	274 (23.3)	215 (16.1)	18 (19.6)
Bulgaria (11 sites)	395 (15.7)	395 (15.8)	173 (14.7)	222 (16.6)	8 (8.7)
Greece (15 sites)	328 (13.1)	328 (13.1)	114 (9.7)	214 (16.0)	1 (1.1)
Croatia (10 sites)	237 (9.4)	237 (9.5)	111 (9.4)	126 (9.4)	20 (21.7)
Spain (9 sites)	167 (6.7)	166 (6.6)	111 (9.4)	56 (4.2)	11 (12.0)
Poland (3 sites)	52 (2.1)	52 (2.1)	19 (1.6)	33 (2.5)	5 (5.4)
Slovenia (4 sites)	42 (1.7)	42 (1.7)	14 (1.2)	28 (2.1)	16 (17.4)
Slovakia (4 sites)	26 (1.0)	26 (1.0)	16 (1.4)	10 (0.7)	3 (3.3)
Romania (3 sites)	23 (0.9)	23 (0.9)	21 (1.8)	2 (0.1)	1 (1.1)

Patients who completed >24 months includes all patients who had >732 days on study, regardless of completion or discontinuation status.
The number of sites administratively closed is 23.
Source: Table 1.1.1

10.2 Descriptive data

10.2.1 Demographics and baseline characteristics

10.2.1.1 Demographics

Patient demographics and baseline characteristics including gender, age, height, weight, and BMI are presented in Table 10-3.

There were slightly more male 1390 (55.7%) than female 1107 (44.3%) patients. The mean (std) age was 69.7 (13.93) years and mean BMI was 26.77 (range: 14.5 to 60.4 kg/m^2).

Table 10-3 Demographics (Safety analysis set)

Characteristic	Binocrit/Epoetin alfa HEXAL (N=2497)
Gender [n (%)]	
Female	1107 (44.3)
Male	1390 (55.7)
Age (years)	
n	2497
Mean (std)	69.7 (13.93)

Characteristic	Binocrit/Epoetin alfa HEXAL (N=2497)
Median	72.0
Q1, Q3	62.0, 80.0
Min, Max	19, 103
Height (cm)	
n	2387
Mean (std)	167.5 (9.41)
Median	168.0
Q1, Q3	160.0, 174.0
Min, Max	138, 200
Nmiss	110
Weight (kg)	
n	2345
Mean (std)	75.26 (17.082)
Median	74.00
Q1, Q3	63.50, 85.00
Min, Max	36.5, 178.6
Nmiss	152
BMI (kg/m^2)	
n	2283
Mean (std)	26.77 (5.432)
Median	25.90
Q1, Q3	23.12, 29.55
Min, Max	14.5, 60.4
Nmiss	214

Source: Table 1.2.1 and Listing 1.1

10.2.1.2 Medical history and current (ongoing) medical conditions

Medical history and current medical conditions (≥5%) by SOC and PT are provided in Table 10- 4.

Prior Medical History

Approximately one quarter of patients had at least one relevant medical history condition.

The most frequently reported SOCs (incidence of ≥5%) for prior medical history events were surgical and medical procedures in 8.7% of patients; neoplasms benign, malignant and unspecified (incl. cysts and polyps) in 6.6% of patients; and cardiac disorders in 5.0% of patients.

No prior medical history PTs were reported in ≥5% of patients. The most frequently reported prior medical history events were cerebrovascular accident and myocardial infarction in 1.8% of patients each.

Current Medical Conditions

Almost all patients had at least one current (ongoing) relevant medical history condition. Relevant ongoing medical history conditions (by SOC and PT) that occurred in at least 5% of patients are summarized in Table 10-4.

The majority (85.7%) of patients had a vascular disorder and more than half (56.0%) had a metabolism and nutrition disorder; cardiac disorders were reported in 41.9% of patients and renal and urinary disorders in 32.7% of patients.

The most frequently reported PTs and SOC (≥5%) for current medical history events were hypertension in 83.1% of patients; diabetes mellitus in 19.3% of patients; Type 2 diabetes mellitus in 19.2% of patients; coronary artery disease and atrial fibrillation in 13.6% of patients; and hyperuricemia in 10.2% of patients.

Table 10-4 Medical history and current medical conditions (≥5%) (Safety analysis set)

System organ class *Preferred term [n (%)]*	**Binocrit/Epoetin alfa HEXAL** **(N=2497)**
Prior medical history	**659 (26.4)**
Surgical and medical procedures	218 (8.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	164 (6.6)
Cardiac disorders	126 (5.0)
Current medical history	**2488 (99.6)**
Vascular disorders	2139 (85.7)
Hypertension	2074 (83.1)
Metabolism and nutrition disorders	1399 (56.0)
Diabetes mellitus	482 (19.3)
Type 2 diabetes mellitus	479 (19.2)
Hyperuricaemia	255 (10.2)
Hyperlipidaemia	163 (6.5)
Dyslipidaemia	143 (5.7)
Hypercholesterolaemia	127 (5.1)
Cardiac disorders	1045 (41.9)
Atrial fibrillation	350 (14.0)
Coronary artery disease	340 (13.6)
Myocardial ischaemia	180 (7.2)
Renal and urinary disorders	816 (32.7)
Glomerulonephritis chronic	194 (7.8)
Endocrine disorders	582 (23.3)
Hyperparathyroidism secondary	323 (12.9)
Hypothyroidism	159 (6.4)

System organ class *Preferred term [n (%)]*	Binocrit/Epoetin alfa HEXAL (N=2497)
Surgical and medical procedures	350 (14.0)
Nervous system disorders	340 (13.6)
Musculoskeletal and connective tissue disorders	335 (13.4)
Respiratory, thoracic and mediastinal disorders	277 (11.1)
Chronic obstructive pulmonary disease	143 (5.7)
Gastrointestinal disorders	267 (10.7)
Infections and infestations	245 (9.8)
Pyelonephritis chronic	137 (5.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	218 (8.7)
Congenital, familial and genetic disorders	188 (7.5)
Reproductive system and breast disorders	165 (6.6)
Benign prostatic hyperplasia	143 (5.7)

Note: Medical history and current medical conditions are coded using MedDRA version 25.1. For each system organ class and preferred term, patients are included only once. At database lock, there was one uncoded medical history term “NOT KNOWN”. This was declared non-codable as it cannot be categorized to any System Organ Class
Source: Table 1.2.3 and Listing 1.3

10.2.1.3 Disease history

Baseline disease history is provided in Table 10-5.

At baseline, most patients had Stage 3, Stage 4, or Stage 5 CKD, with approximately half (52.5%) of the patients having Stage 5 CKD.

The primary causes of CKD were most commonly hypertension (31.7% of patients) or diabetes (25.8% of patients).

Less than half of the patients were on dialysis (1090 patients [43.7%]) at baseline. Of these, most were on hemodialysis (959 patients [88.0%]).

Most patients had Grade 1 (64.5%) or Grade 2 (31.8%) renal anemia.

Table 10-5 Baseline disease history (Safety analysis set)

	Binocrit/Epoetin alfa HEXAL (N=2497)
CKD diagnosis	
Primary mechanism of CKD [n (%)]	
Chronic glomerulonephritis	292 (11.7)
Diabetes mellitus	645 (25.8)

	Binocrit/Epoetin alfa HEXAL (N=2497)
Hypertension	792 (31.7)
Interstitial nephritis	154 (6.2)
Polycystic kidney disease	123 (4.9)
Other[a]	490 (19.6)
Missing	1
Stage of CKD [n (%)]	
Stage 1	19 (0.8)
Stage 2	27 (1.1)
Stage 3	442 (17.7)
Stage 4	706 (28.3)
Stage 5	1302 (52.2)
Missing	1
Time since diagnosis of CKD (years)	
n	2333
Mean (std)	7.05 (7.723)
Median	4.7
Q1, Q3	1.68, 9.67
Min, Max	<0.1, 58.9
Nmiss	164
Renal anemia diagnosis	
Severity of renal anemia [n (%)]	
Grade 1	1606 (64.5)
Grade 2	793 (31.8)
Grade 3	86 (3.5)
Grade 4	6 (0.2)
Missing	6
Time since diagnosis of renal anemia (years)	
n	2307
Mean (std)	2.62 (3.652)
Median	1.22
Q1, Q3	0.34, 3.38
Min, Max	<0.1, 33.1
Nmiss	190
Hospitalization due to serious infections during the last 12 months prior to informed consent [n (%)]	
Yes	208 (8.7)
No	2196 (91.3)
Missing	93
Patients on dialysis [n (%)]	
Yes	1090 (43.7)

	Binocrit/Epoetin alfa HEXAL (N=2497)
No	1406 (56.3)
Missing	1
Current dialysis type[b] [n (%)]	
Hemodialysis	959 (88.0)
Peritoneal Dialysis	131 (12.0)
Time since start of current dialysis (years)	
n	1088
Mean (std)	2.68 (3.498)
Median	1.28
Q1, Q3	0.38, 3.70
Min, Max	-0.02, 28.77
Nmiss	2
Time since start of initial dialysis (years)	
n	1089
Mean (std)	3.57 (5.196)
Median	1.65
Q1, Q3	0.53, 4.51
Min, Max	-0.02, 41.57
Nmiss	1

a. Other includes Cancer, Nephrosclerosis, Chronic pyelonephritis, Obstructive uropathy, Cardio-renal disease, Toxicity / Drug induced nephropathy, Nephroangiosclerosis, Kidney shrinking/dysplasia, Hereditary disease, Combined–Multiple factors, Unknown reason.
b. Percentages are based on the number of patients on dialysis.
Stage 1 = Kidney damage with normal or increased GFR: ≥90 (mL/min per 1.73 m^2);
Stage 2 = Kidney damage with mild decreased GFR: 60-89 (mL/min per 1.73 m^2);
Stage 3 = Moderate kidney damage with decreased GFR: 30-59 (mL/min per 1.73 m^2);
Stage 4 = Severe kidney damage with decreased GFR: 15-29 (mL/min per 1.73 m^2);
Stage 5 = Kidney failure: GFR < 15 (mL/min per 1.73 m^2) or dialysis.
Severity of renal anemia: Grade 1 = Hemoglobin 10.0 g/dL to <LLN;
Grade 2 = Hemoglobin 8.0 g/dL to 10.0 g/dL;
Grade 3 = Hemoglobin <8.0 g/dL, transfusion indicated;
Grade 4 = Life-threatening consequences, urgent intervention indicated.
Note: Durations are calculated from event date (diagnosis of CKD/renal anemia, start of current/initial dialysis) to ICF date. If the date of an event equals the ICF date (e.g., due to partial date imputation) duration is shown as 0.
Negative durations are due to initial/current dialysis events that started between ICF and Visit 1 date.
Source: Table 1.2.2 and Listing 1.2

10.2.1.4 Prior use of ESA

Patients with prior use of ESAs are provided in Table 10-6.

Approximately one third of the patients (37.0%) had previously received ESAs. The most frequently (≥10%) used ESAs were epoetin zeta in 284 patients (30.8%), epoetin alfa in 276 patients (29.9%), and darbepoetin alfa in 195 patients (21.1%).

Table 10-6 Prior use of erythropoiesis-stimulating agent (Safety analysis set)

Preferred Term [n (%)]	Binocrit/Epoetin alfa HEXAL (N=2497)
Patients with prior use of ESA [n (%)]	923 (37.0)
Time since first ESA treatment (years)	
n	906
Mean (std)	3.51 (3.522)
Median	2.52
Q1, Q3	1.10, 4.63
Min, Max	<0.1, 24.3
Nmiss	17
Generic name (trade name) of last prior ESA[a] [n (%)]	
Epoetin zeta	284 (30.8)
Epoetin alfa	276 (29.9)
Darbepoetin alfa	195 (21.1)
Epoetin beta	63 (6.8)
Methoxy polyethylene glycol-epoetin beta	58 (6.3)
Erythropoietin	23 (2.5)
Epoetin theta	18 (2.0)
Other antianaemic preparations	4 (0.4)
*Daprodustat	1 (0.1)
*Roxadustat	1 (0.1)
Route of last prior ESA[a] [n (%)]	
Subcutaneous	582 (63.1)
Intravenous	331 (35.9)
Missing	10

Note: WHO Drug Dictionary Version 2022SEP was used to code ESA trade names.
a. Percentages are based on the number of patients with prior use of ESA.
Note: Durations are calculated from event date (first ESA treatment) to ICF date. If the date of an event equals the ICF date (e.g., due to partial date imputation) duration is shown as 0.
*During the CSR review, it was identified that there were 2 patients (although for whom the study investigator physician considered that all inclusion criteria and none of the exclusion criteria were met) should not have been included in the study as they met the exclusion criteria of 'History of treatment with an erythropoietin/ESA product which is not authorized in the EU'. However, the sponsor decided to transparently keep those data including safety data in the report. Therefore, 2 protocol deviations were added to the CSR.
Source: Table 1.2.4 and Listing 5.3

10.2.1.5 Prior medications

Prior medications are presented in Table 10-7.

Prior medications were reported for less than 3% of the patients. The prior medication reported most was ramipril in 7 patients (0.3%). Of note, concomitant medications are mentioned in Section 10.2.3.3 below.

Table 10-7 Prior medications (≥0.1%) (Safety analysis set)

Preferred Term [n (%)]	Binocrit/Epoetin alfa HEXAL (N=2497)
Any Medications	67 (2.7)
Ramipril	7 (0.3)
Alfacalcidol	4 (0.2)
Atorvastatin	4 (0.2)
Furosemide	4 (0.2)
Torasemide	4 (0.2)
All other non-therapeutic products	3 (0.1)
Allopurinol	3 (0.1)
Ceftriaxone sodium	3 (0.1)
Ciprofloxacin	3 (0.1)
Apixaban	2 (0.1)
Calcium gluconate	2 (0.1)
Colecalciferol	2 (0.1)
Ferrous sulfate	2 (0.1)
Metamizole sodium	2 (0.1)
Moxonidine	2 (0.1)
Paricalcitol	2 (0.1)
Pravastatin	2 (0.1)
Spironolactone	2 (0.1)
Trandolapril	2 (0.1)
Valsartan	2 (0.1)
Warfarin	2 (0.1)

Note: Medications with an end date before informed consent are considered prior, otherwise concomitant.
Note: WHO Drug Dictionary Version 2022SEP was used to code prior and concomitant medications.
Source: Table 4.2.3 and Listing 5.5

10.2.2 Protocol deviations

Protocol deviations are provided in Table 10-8.

Overall, PDs were reported in 534 patients (21.4%). The most commonly (≥10%) reported PDs were delayed SAE/AESI/pregnancy reporting by site in 275 patients (11.0%) all of which were assessed and those confirmed as reportable were finally included in the safety database and considered for analysis. Informed consent deviations were reported in 206 patients (8.2%). Each deviation related to informed consent was assessed, most of which were minor in nature and

not impacting the validity of the informed consent (136 deviations). Those identified as major were either properly addressed and resolved (11 deviations) or did not represent an informed consent deviation (74 deviations). The latter were related to a delayed documentation of the patient consenting into the medical source data, but documentation was completed.

Table 10-8 Protocol deviations (Safety analysis set)

Protocol deviations Category [n (%)]	Binocrit/Epoetin alfa HEXAL (N=2497)
Any protocol deviation	534 (21.4)
SAE/AESI/pregnancy reporting	275 (11.0)
Informed consent	206 (8.2)
Patient observation more than 24 months	92 (3.7)
In/Exclusion criteria	14 (0.6)
Other*:	1 (<0.1)
B)	1 (<0.1)
A)	0
C)	0

Note: For each category, patients are included only once, even if they experienced multiple deviation events in a category.
*: A) Any data resulting in exclusion from the analysis when data integrity/reliability cannot be confirmed.
B) Any eCRF pages not signed at database lock.
C) Any protocol deviation upgraded from the classification “clarification” to “protocol deviation” which the HEXAL AG&ICON team assessed as “relevant for CSR”.
Note: Protocol deviations related to re-consent were excluded from the analysis.
Source: Table 1.2.5 and Listing 1.4

10.2.3 Treatment regimen, compliance, and exposure to drug

10.2.3.1 Study drug treatment

10.2.3.1.1 Summary of exposure to study drug

The exposure to s.c. HX575 is provided in Table 10-9.

Overall, 1587 patients (63.6%) received Binocrit while 917 patients (36.7%) received Epoetin alfa HEXAL. The total documented patient exposure was 3600.2 years. The median treatment duration was 1.82 years.

Table 10-9 Summary of exposure to study drug (Safety analysis set)

	Binocrit/Epoetin alfa HEXAL (N=2497)
HX575 tradename [n (%)]	
Binocrit	1587 (63.6)
Epoetin alfa Hexal	917 (36.7)
Treatment duration during the study (years)	
n	2497

	Binocrit/Epoetin alfa HEXAL (N=2497)
Mean (std)	1.44 (0.656)
Median	1.82
Q1, Q3	0.86, 1.98
Min, Max	<0.1, 2.6
Patient exposure years	3600.2
Duration since first subcutaneous HX575 treatment (years)	
n	2485
Mean (std)	2.01 (1.209)
Median	2.00
Q1, Q3	1.32, 2.36
Min, Max	<0.1, 13.1
Nmiss	12
Overall HX575 dose (kIU)	
n	2445
Mean (std)	519.6 (531.57)
Median	372.0
Q1, Q3	180.9, 661.1
Min, Max	<1, 9377
Nmiss	52
Overall HX575 dose (IU/kg)	
n	2309
Mean (std)	7233.43 (7141.084)
Median	5064.29
Q1, Q3	2420.17, 9556.67
Min, Max	3.6, 72410.7
Nmiss	188
Frequency of HX575 intake [n (%)]	
Three times per week	810 (32.4)
Twice per week	946 (37.9)
Once per week	1480 (59.3)
Once every two weeks	491 (19.7)
Monthly	161 (6.4)
Daily	0
As necessary	44 (1.8)
Unknown	1 (<0.1)
Other	327 (13.1)

Note: A patient may have more than one HX575 tradename or frequency of HX575 intake. Treatment duration during the study is calculated as: ([Date of Last Exposure to Treatment – Date of ICF + 1]/365.25). Duration since first subcutaneous HX575 treatment is calculated as: ([Date of Last Exposure to Treatment – Date of first subcutaneous HX575 treatment + 1]/365.25).
Source: Table 4.1.1 and Listing 5.1

10.2.3.1.2 Weekly epoetin dosage over time (secondary endpoint)

Weekly s.c. HX575 dosage (IU/kg and kIU) by visit (Visit 1 to Visit 7) for patients are provided in Table 10-10. The mean (std) weekly dosage of s.c. HX575 over time remained consistent (Visit 1 to Visit 7).

Table 10-10 Weekly HX575 dosage by visit (Safety analysis set)

Time Point	Binocrit/Epoetin alfa HEXAL (N=2497)
Parameter: weekly HX575 dose (kIU)	
Visit 1	
n	2443
Mean (std)	7.07 (5.570)
Median	6.00
Q1,Q3	3.00, 10.00
Min, Max	0.0, 40.0
Nmiss	54
Visit 2	
n	2192
Mean (std)	6.94 (5.623)
Median	5.65
Q1,Q3	3.00, 9.00
Min, Max	0.0, 49.6
Nmiss	49
Visit 3	
n	1964
Mean (std)	6.48 (5.617)
Median	5.00
Q1,Q3	2.89, 8.00
Min, Max	0.0, 53.2
Nmiss	66
Visit 4	
N	1733
Mean (std)	6.51 (5.754)
Median	5.00
Q1, Q3	2.62, 8.52
Min, Max	0.0, 46.7
Nmiss	64
Visit 5	
n	1573
Mean (std)	6.48 (5.821)

Time Point	Binocrit/Epoetin alfa HEXAL (N=2497)
Median	4.92
Q1, Q3	2.57, 8.20
Min, Max	0.0, 56.0
Nmiss	59
Visit 6	
n	1418
Mean (std)	6.77 (5.985)
Median	5.00
Q1,Q3	2.80, 9.00
Min, Max	0.0, 40.0
Nmiss	50
Visit 7	
n	1299
Mean (std)	6.85 (5.967)
Median	5.00
Q1, Q3	3.00, 9.00
Min, Max	0.0, 40.0
Nmiss	56
Parameter: weekly HX575 dose (IU/kg)	
Visit 1	
n	2292
Mean (std)	99.12 (84.063)
Median	72.73
Q1, Q3	42.55, 130.43
Min, Max	0.0, 625.0
Nmiss	205
Visit 2	
n	2081
Mean (std)	96.25 (80.644)
Median	71.30
Q1, Q3	40.82, 125.00
Min, Max	0.0, 625.0
Nmiss	160
Visit 3	
n	1870
Mean (std)	88.54 (78.343)
Median	66.09

Time Point	Binocrit/Epoetin alfa HEXAL (N=2497)
Q1,Q3	35.71, 113.21
Min, Max	0.0, 625.0
Nmiss	160
Visit 4	
n	1668
Mean (std)	88.92 (79.990)
Median	65.84
Q1, Q3	35.46, 115.76
Min,Max	0.0, 625.0
Nmiss	129
Visit 5	
n	1518
Mean (std)	88.87 (80.302)
Median	64.94
Q1, Q3	35.09, 115.94
Min,Max	0.0, 717.9
Nmiss	114
Visit 6	
n	1382
Mean (std)	93.00 (84.043)
Median	67.92
Q1, Q3	37.13, 120.30
Min,Max	0.0, 819.8
Nmiss	86
Visit 7	
n	1265
Mean (std)	94.24 (84.405)
Median	68.18
Q1,Q3	38.10, 121.21
Min, Max	0.0, 833.3
Nmiss	90

Source: Table 2.3 and Listing 5.2

10.2.3.2 Iron supplementation (other endpoint)

Iron supplementation by PT is provided in Table 10-11.

More than half of the patients received iron supplementation (1740 patients [69.7%]). The most frequently (≥10%) received iron supplementations were saccharated iron oxide in 509 patients (20.4%) and ferric carboxymaltose in 358 patients (14.3%).

Table 10-11 Iron supplementation by preferred term (≥5%) (Safety analysis set)

Preferred term [n (%)]	Binocrit/Epoetin alfa HEXAL (N=2497)
Any iron supplementation	1740 (69.7)
Saccharated iron oxide	509 (20.4)
Ferric carboxymaltose	358 (14.3)
Ferric sodium gluconate complex	248 (9.9)
Ferrous sulfate	162 (6.5)
Iron dextran	145 (5.8)
Ferrous glycine sulfate	127 (5.1)

Note: WHO Drug Dictionary Version 2022SEP was used to code iron supplementations.
Source: Table 4.2.2 and Listing 5.4

Iron supplementation by visit is provided in Table 10-12.

Approximately half of the patients were receiving iron supplementation at Visit 1. At each of the subsequent visits, at least 45% of the patients received iron supplementation.

Table 10-12 Number of patients with iron supplementation by visit (Safety analysis set)

Time point [n (%)]	Binocrit/Epoetin alfa HEXAL (N=2497)
Visit 1	2497
Number of patients with iron supplementation	1330 (53.3)
Visit 2	2242
Number of patients with iron supplementation	1076 (48.0)
Visit 3	2030
Number of patients with iron supplementation	927 (45.7)
Visit 4	1799
Number of patients with iron supplementation	824 (45.8)
Visit 5	1633
Number of patients with iron supplementation	739 (45.3)
Visit 6	1468
Number of patients with iron supplementation	675 (46.0)
Visit 7	1355
Number of patients with iron supplementation	616 (45.5)

Note: Percentages are based on the number of patients at each visit.
Source: Table 4.2.1 and Listing 5.4

10.2.3.3 Concomitant medications

Concomitant medications are included in Table 10-13.

Almost all patients received concomitant medications at least once during the study (2434 patients [97.5%]). The most frequently (≥30%) reported concomitant medications included furosemide in 847 patients (33.9%) and acetylsalicylic acid in 750 patients (30.0%).

Table 10-13 Concomitant medications (≥5%) (Safety analysis set)

Preferred Term [n (%)]	Binocrit/Epoetin alfa HEXAL (N=2497)
Any medications	2434 (97.5)
Furosemide	847 (33.9)
Acetylsalicylic acid	750 (30.0)
Allopurinol	638 (25.6)
Torasemide	567 (22.7)
Amlodipine	503 (20.1)
Colecalciferol	455 (18.2)
Bisoprolol	443 (17.7)
Pantoprazole	434 (17.4)
Atorvastatin	408 (16.3)
Folic acid	408 (16.3)
Paricalcitol	329 (13.2)
Calcitriol	326 (13.1)
Covid-19 vaccine	286 (11.5)
Sodium bicarbonate	277 (11.1)
Ramipril	275 (11.0)
Doxazosin	254 (10.2)
Moxonidine	245 (9.8)
Bisoprolol fumarate	225 (9.0)
Simvastatin	224 (9.0)
All other non-therapeutic products	221 (8.9)
Omeprazole	220 (8.8)
Metoprolol	204 (8.2)
Sevelamer	201 (8.0)
Calcium carbonate	200 (8.0)
Insulin glargine	200 (8.0)
Carvedilol	189 (7.6)
Alfacalcidol	187 (7.5)
Febuxostat	183 (7.3)
Clopidogrel	174 (7.0)
Sevelamer carbonate	167 (6.7)
Candesartan	163 (6.5)
Lercanidipine	157 (6.3)
Levothyroxine	154 (6.2)
Nebivolol	139 (5.6)
Levothyroxine sodium	133 (5.3)

Note: Medications with an end date before informed consent are considered prior, otherwise concomitant.
Note: WHO Drug Dictionary Version 2022SEP was used to code prior and concomitant medications
Source: Table 4.2.3 and Listing 5.5

10.3 Outcome data

The study was conducted to add further evidence regarding the safe use of s.c. HX575 in patients with CKD-induced anemia who received s.c. treatment and by monitoring closely the AE profile under real-life conditions.

Overall, 2510 eligible patients were enrolled in the study of which 2497 patients were included in the SAF. The summary statistics of the following main results are calculated on the basis of the SAF.

10.4 Main results

10.4.1 Primary endpoint

The primary endpoint was defined as the incidence of any AESIs (see Section 9.4.1). AESIs included any PRCA or LOE cases, if applicable.

10.4.1.1 Any adverse events of special interest

AESIs (≥1%) by category, SOC, and PT are presented in Table 10-14.

AESIs were reported in 429 patients (17.2% [95% CI: 15.7, 18.7]), with an IR (per 1000 patient years) of 126 (95% CI: 115, 139). An overall summary of AESIs by severity and outcome is provided in Table 10-25.

PRCA

No events of PRCA were reported in any of the patients during the study.

LOE

An AESI of LOE was reported in 1 patient.

Narrative description for patient PPD **:**

This patient started treatment with s.c. HX575 in PPD and was enrolled in the study on PPD. The LOE was reported 7 days after the patient's start in the study. During the time when LOE was reported, the patient was suffering from gastric hemorrhage which resulted in blood loss and anemia (decrease in hemoglobin). The investigator did not collect blood for ADA assessment. The LOE event resolved in PPD (at an unrecorded date).

The s.c. HX575 was discontinued from Day 82 (PPD) to Day 112 (PPD). The interruption of s.c. HX575 was approximately 3 months after LOE was reported. The reason for interruption was not available. Reticulocyte count and iron/transferrin saturation were not available. The patient did not receive any transfusion or prior iron supplementation. No concomitant medications were reported. Ferritin levels showed a decline at 25 ng/mL on Day 101 (PPD) which later on increased to 82 ng/mL on Day 228 (PPD); a reason for the increase in ferritin levels was not recorded. The patient resumed study treatment and the dose was increased from 5 kIU QW to 10 kIU BIW. The patient completed the study on PPD.

Sponsor's assessment: The Sponsor's medical experts did not consider this as a confirmed LOE case, as the cause of the decrease in hemoglobin values was due to foregoing blood loss.

Moreover, after an interruption of approximately 1 month, HX575 treatment was resumed and was effective for the remainder of study.

Other AESIs

The most frequently reported AESIs were major thromboembolic and cardiovascular events in 163 patients (6.5% [95% CI: 5.6, 7.6]) with an IR (per 1000 patient years) of 46 (95% CI: 39, 53); congestive heart failure in 119 patients (4.8% [95% CI: 4.0, 5.7]) with an IR of 33 (95% CI: 27, 39); and hypertension (worsening or newly developing hypertension, hypertensive crisis, uncontrolled hypertension) in 49 patients (2.0% [95% CI: 1.5, 2.6]) with an IR of 13 (95% CI: 10, 18).

The most frequently reported AESIs by SOC were cardiac disorders (AESI: congestive heart failure) with an IR (per 1000 patient years) of 32 (95% CI: 27, 39); neoplasms benign, malignant and unspecified (incl cysts and polyps) with an IR of 21 (95% CI: 17, 26); and cardiac disorders (AESI: major thromboembolic and cardiovascular events) with an IR of 19 (95% CI: 15, 25)

The most frequently reported AESIs by PT were cardiac failure with an IR (per 1000 patient years) of 18 (95% CI: 14, 23); hyperkalemia with an IR of 19 (95% CI: 15, 24); and hypertension with an IR of 10 (95% CI: 7, 13).

No patient experienced posterior reversible encephalopathy syndrome.

Table 10-14 Adverse events of special interest by category, including system organ class and preferred term (Safety analysis set)

AESI category	**Binocrit/Epoetin alfa HEXAL (N=2497)**			
System organ class *Preferred term*	**n**	**E**	**% (95% Clopper-Pearson CI)**	**IR (95% CI)**
PRCA–AESI	0	0	-	-
Lack of efficacy–AESI	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Major thromboembolic and cardiovascular events–AESI	163	207	6.5 (5.6, 7.6)	46 (39, 53)
Cardiac disorders	71	84	2.8 (2.2, 3.6)	19 (15, 25)
Nervous system disorders	43	48	1.7 (1.2, 2.3)	12 (9, 16)
Injury, poisoning and procedural complications	38	57	1.5 (1.1, 2.1)	10 (8, 14)
Congestive heart failure-AESI	119	141	4.8 (4.0, 5.7)	33 (27, 39)
Cardiac disorders	118	138	4.7 (3.9, 5.6)	32 (27, 39)
Cardiac failure	66	79	2.6 (2.0, 3.4)	18 (14, 23)
Cardiac failure acute	29	30	1.2 (0.8, 1.7)	8 (5, 11)
Hypertension (worsening or newly developing hypertension, hypertensive crisis, uncontrolled hypertension)-AESI	49	54	2.0 (1.5, 2.6)	13 (10, 18)
Vascular disorders	44	49	1.8 (1.3, 2.4)	12 (9, 16)
Hypertension	35	38	1.4 (1.0, 1.9)	10 (7, 13)
Seizures-AESI	5	6	0.2 (0.1, 0.5)	1 (1, 3)
Posterior reversible encephalopathy syndrome-AESI	0	0	-	-

AESI category	Binocrit/Epoetin alfa HEXAL (N=2497)			
System organ class *Preferred term*	n	E	% (95% Clopper-Pearson CI)	IR (95% CI)
Blood disorders (white blood cell lineage disorders, thrombocythemia and porphyria-AESI	9	10	0.4 (0.2, 0.7)	2 (1, 5)
***De novo* malignancies, unexpected tumor growth-AESI**	80	111	3.2 (2.5, 4.0)	22 (18, 27)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	76	105	3.0 (2.4, 3.8)	21 (17, 26)
Hypersensitivity reactions, anaphylaxis incl. serious skin reactions-AESI	3	3	0.1 (<0.1, 0.4)	1 (<1, 3)
Hyperkalemia-AESI	69	81	2.8 (2.2, 3.5)	19 (15, 24)
Metabolism and nutrition disorders	68	80	2.7 (2.1, 3.4)	19 (15, 24)
Hyperkalaemia	68	80	2.7 (2.1, 3.4)	19 (15, 24)

n = Number of patients; E = Number of events; IR = Incidence Rate per 1000 patient years; PRCA = Not applicable.
Note: Adverse events were coded using MedDRA version 25.1. For each system organ class and preferred term, patients are included only once, even if they experienced multiple events in that system organ class or preferred term.
Incidence rate was calculated using a Poisson distribution model with the number of patients with each AE offset by the sum of patient years for all patients. Patient years was calculated as the sum of duration of risk ([date of the AE or end of study date [if no AE occurred] - informed consent date + 1]/365.25) for each patient. For this in-text table, a cut-off of ≥1% was applied to system organ class and preferred terms, while all AESI categories are presented without cut-off.
Source: Table 3.2.1 and Listing 2.4

10.4.1.2 Serious adverse events of special interest

Serious AESI (≥1%) by category, SOC, and PT are provided in Table 10-15.

Serious AESI were reported in 328 patients (13.1% [95% CI: 11.8, 14.5]), with an IR (per 1000 patient years) of 94 (95% CI: 84, 104) (Table 10-25).

The most frequently reported serious AESIs were major thromboembolic and cardiovascular events in 144 patients (5.8% [95% CI: 4.9, 6.8]) with an IR (per 1000 patient years) of 40 (95% CI: 34, 47); congestive heart failure in 113 patients (4.5% [95% CI: 3.7, 5.4]) with an IR of 31 (95% CI: 26, 37); and de novo malignancies or unexpected tumor growth in 68 patients (2.7% [95% CI: 2.1, 3.4]) with an IR of 19 (95% CI: 15, 24).

The most frequently reported serious AESIs by SOC were cardiac disorders (AESI: congestive heart failure) with an IR (per 1000 patient years) of 31 (95% CI: 26, 37); cardiac disorders (AESI: major thromboembolic and cardiovascular events) with an IR of 18 (95% CI: 14, 23), and neoplasms benign, malignant and unspecified (incl cysts and polyps) with an IR of 18 (95% CI: 14, 23).

The most frequently reported serious AESIs by PT were cardiac failure with an IR (per 1000 patient years) of 18 (95% CI: 14, 22) and cardiac failure acute with an IR of 8 (95% CI: 5, 11) for the AESI of congestive heart failure.

Table 10-15 Serious adverse events of special interest by category, including system organ class and preferred term (Safety analysis set)

AESI category-Primary Endpoint	**Binocrit/Epoetin alfa HEXAL (N=2497)**			
System organ class *Preferred term*	**n**	**E**	**% (95% Clopper-Pearson CI)**	**IR (95% CI)**
PRCA–AESI	0	0	-	-
Lack of efficacy–AESI	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Major thromboembolic and cardiovascular events –AESI	144	174	5.8 (4.9, 6.8)	40 (34, 47)
Cardiac disorders	65	77	2.6 (2.0, 3.3)	18 (14, 23)
Nervous system disorders	41	45	1.6 (1.2, 2.2)	11 (8, 15)
Injury, poisoning and procedural complications	28	38	1.1 (0.7, 1.6)	8 (5, 11)
Congestive heart failure-AESI	113	131	4.5 (3.7, 5.4)	31 (26, 37)
Cardiac disorders	112	129	4.5 (3.7, 5.4)	31 (26, 37)
Cardiac failure	64	76	2.6 (2.0, 3.3)	18 (14, 22)
Cardiac failure acute	29	30	1.2 (0.8, 1.7)	8 (5, 11)
Hypertension (worsening or newly developing hypertension, hypertensive crisis, uncontrolled hypertension)-AESI	20	20	0.8 (0.5, 1.2)	5 (4, 8)
Seizures-AESI	5	6	0.2 (0.1, 0.5)	1 (1, 3)
Posterior reversible encephalopathy syndrome-AESI	0	0	-	-
Blood disorders (white blood cell lineage disorders, thrombocythemia and porphyria-AESI	3	3	0.1 (<0.1, 0.4)	1 (<1, 3)
Denovo malignancies, unexpected tumor growth- AESI	68	91	2.7 (2.1, 3.4)	19 (15, 24)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	66	89	2.6 (2.0, 3.4)	18 (14, 23)
Hypersensitivity reactions, anaphylaxis incl. serious skin reactions-AESI	0	0	-	-

n = Number of patients; E = Number of events; IR = Incidence Rate per 1000 patient years; PRCA = Not applicable.
Note: Adverse events were coded using MedDRA version 25.1. For each system organ class and preferred term, patients are included only once, even if they experienced multiple events in that system organ class or preferred term.
Incidence rate was calculated using a Poisson distribution model with the number of patients with each AE offset by the sum of patient years for all patients. Patient years was calculated as the sum of duration of risk ([date of the AE or end of study date [if no AE occurred] - informed consent date + 1]/365.25) for each patient. For this in-text table, a cut-off of ≥1% was applied to system organ class and preferred term, while all AESI categories are presented without cut-off.
Source: Table 3.2.2

10.4.1.3 Adverse events of special interest related to study drug

AESIs related to s.c. HX575 by category, SOC, and PT are provided in Table 10-16.

Related AESIs were reported in 15 patients (0.6% [95% CI: 0.3, 1.0]), with an IR (per 1000 patient years) of 4 (95% CI: 2, 7) (Table 10-25).

The most frequently reported related AESIs were major thromboembolic and cardiovascular events in 4 patients (0.2% [95% CI: <0.1, 0.4]) with an IR (per 1000 patient years) of 1 (95% CI: <1, 3); congestive heart failure in 1 patient (<0.1% [95% CI: <0.1, 0.2]) with an IR of <1 (95% CI: <1, 2); and hypertension (worsening or newly developing hypertension, hypertensive crisis, uncontrolled hypertension) in 8 patients (0.3% [95% CI: 0.1, 0.6]) with an IR of 2 (95% CI: 1, 4).

The AESIs of vascular disorders (SOC) were reported with an IR (per 1000 patient years) of 2 (95% CI: 1, 4); and nervous system disorders with an IR of 1 (95% CI: <1, 2). The remaining AESIs had an IR of <1 (95% CI: <1, 2).

The AESI of hypertension (PT) were reported with an IR (per 1000 patient years) of 2 (95% CI: 1, 4). The remaining AESIs had an IR of <1 95% CI: <1, 2]).

Thromboemoblic events, hypertension, hypersensitivity reaction and hyperkalemia are known ADRs for Epoetin alfa and listed in SmPC. Other related AESIs are further described below:

Narrative description of AESIs with a suspected causal relationship to s.c. HX575 (which are not known ADRs)

Patient ID PPD was a PPD-year-old PPD who had serious AESI (severe) of cerebral ischemia on Day 132 (PPD). The patient's current medical conditions included PPD, PPD PPD PPD, PPD PPD, PPD, PPD and PPD Concomitant medications included PPD allopurinol, pregabalin, acetylsalicylic acid, PPD PPD folic acid, PPD, PPD, calcium carbonate, alfacalcidol, beclometasone, furosemide, sevelamer, PPD and PPD On Day 134 (PPD), the patient died due to this event.

Patient ID PPD was a PPD-year-old PPD who had serious AESI (severe) of hemorrhage intracranial on Day 684 (PPD). The patient had a medical history of PPD PPD, PPD, PPD, PPD and PPD; current medical conditions included PPD PPD and PPD Concomitant medications included prednisone, allopurinol, PPD, calcitriol, colecalciferol, omega-3 triglycerides, pantoprazole, sodium bicarbonate, PPD, PPD and PPD On Day 703 (PPD), the patient died due to this event.

Patient ID PPD was a PPD-year-old PPD who had serious related AESIs (severe) of cardiac failure and pulmonary embolism on Day 105 (PPD). On the same day, the patient also had severe SAEs of pneumonia, sepsis, and pulmonary infarction which were not considered as related to s.c. HX575-507. The patient had a medical history of PPD; current medical conditions included PPD, PPD PPD PPD PPD PPD PPD PPD, PPD and PPD. No concomitant

medications were reported. Treatment for pulmonary infarction included meropenem. On Day 106 (PPD), the patient died due to cardiac failure, pneumonia, sepsis, pulmonary infarction, and pulmonary embolism.

Patient ID PPD was a PPD-year-old PPD who had serious AESI (moderate) of breast neoplasm on an unknown date in PPD. Historical conditions including any history of PPD was not known. Current medical conditions included PPD and PPD Concomitant medications included PPD and PPD The dose of s.c. HX575-507 was adjusted. The event resolved on Day 649 (PPD) following surgical removal of the tumor.

Patient ID PPD was a PPD-year-old PPD who had AESI (moderate) of drug reaction with eosinophilia and systemic symptoms on Day 14 (PPD). Current medical condition included PPD. Concomitant medications included clopidogrel, PPD PPD, and furosemide. S.C. HX575-507 was permanently discontinued due to this event. The event resolved on Day 15 (PPD).

Multiple underlying comorbid conditions (including old age in most of the patients) and concurrent medications are confounding factors for the events described above.

Table 10-16 Adverse events of special interest related to study drug by category, including system organ class and preferred term (Safety analysis set)

AESI Category	Binocrit/Epoetin alfa HEXAL (N=2497)			
System organ class *Preferred term*	n	E	% (95% Clopper-Pearson CI)	IR (95% CI)
PRCA–AESI	0	0	-	-
Lack of Efficacy–AESI	0	0	-	-
Major thromboembolic and cardiovascular events –AESI	4	5	0.2 (<0.1, 0.4)	1 (<1, 3)
Nervous system disorders	2	2	0.1 (<0.1, 0.3)	1 (<1, 2)
Cerebral ischaemia	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Haemorrhage intracranial	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Injury, poisoning and procedural complications	1	2	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Arteriovenous graft thrombosis	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Vascular graft thrombosis	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Respiratory, thoracic and mediastinal disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Pulmonary embolism	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Congestive heart failure–AESI	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Cardiac disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Cardiac failure	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Hypertension (worsening or newly developing hypertension, hypertensive crisis, uncontrolled hypertension)–AESI	8	8	0.3 (0.1, 0.6)	2 (1, 4)
Vascular disorders	8	8	0.3 (0.1, 0.6)	2 (1, 4)
Hypertension	6	6	0.2 (0.1, 0.5)	2 (1, 4)

AESI Category	Binocrit/Epoetin alfa HEXAL (N=2497)			
System organ class *Preferred term*	n	E	% (95% Clopper-Pearson CI)	IR (95% CI)
Accelerated hypertension	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Hypertensive crisis	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Seizures–AESI	0	0	-	-
Posterior Reversible Encephalopathy Syndrome–AESI	0	0	-	-
Blood disorders (white blood cell lineage disorders, thrombocythemia and porphyria)–AESI	0	0	-	-
Denovo malignancies, unexpected tumor growth–AESI	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Breast neoplasm	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Hypersensitivity reactions, anaphylaxis incl. serious skin reactions–AESI	2	2	0.1 (<0.1, 0.3)	1 (<1, 2)
Immune system disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Hypersensitivity	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Skin and subcutaneous tissue disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Drug reaction with eosinophilia and systemic symptoms	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Hyperkalemia–AESI	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Metabolism and nutrition disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Hyperkalaemia	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)

n = Number of patients; E = Number of events; IR = Incidence Rate per 1000 patient years; PRCA = Not applicable.
Note: Adverse events were coded using MedDRA version 25.1. For each system organ class and preferred term, patients are included only once, even if they experienced multiple events in that system organ class or preferred term.
Incidence rate was calculated using a Poisson distribution model with the number of patients with each AE offset by the sum of patient years for all patients. Patient years was calculated as the sum of duration of risk ([date of the AE or end of study date [if no AE occurred] - informed consent date + 1]/365.25) for each patient.
Source: Table 3.2.3 and Listing 2.4

10.4.1.4 Serious adverse events of special interest related to study drug

Serious AESIs related to s.c. HX575 by time in study until the event, PT, action taken, and outcome are provided in Table 10-17.

Related serious AESI were reported in 6 patients (0.2% [95% CI: 0.1, 0.5]), with an IR (per 1000 patient years) of 2 (95% CI: 1, 4) (Table 10-25).

Table 10-17 Related serious adverse events of special interest

Patient ID/Age/Gender	Days in study until AE[a]	Preferred term	Action taken[b]	Outcome
PPD /PPD/	132	Cerebral ischaemia	-	Fatal
PPD /PPD/	78	Hypertensive crisis	3	Recovering/Resolving
	684	Haemorrhage intracranial	-	Fatal
PPD /PPD/	105	Cardiac failure	3,4	Fatal
	105	Pulmonary embolism	3,4	Fatal
PPD /PPD/	-	Breast neoplasm	1	Recovered/Resolved
PPD /PPD/	109	Hypertension	1,4	Recovered/Resolved
PPD /PPD/	-	Hypertension	1,3	Recovered/Resolved

- = Not applicable
a. Days in study until AE is only calculated for complete AE start dates.
b. Action taken with study drug: 1 = Drug of interest dose adjusted/temporarily interrupted; 2 = Drug of interest permanently discontinued due to this AE; 3 = Adverse event treatment medication introduced or adjusted; 4 = Non-drug therapy given; 5 = Other.
Source: Listing 2.2.1

10.4.2 Secondary and other endpoints

10.4.2.1 Safety evaluation

10.4.2.1.1 Incidence of serious adverse events

The incidence of SAEs is described in Section 10.6.

10.4.2.1.2 Incidence of adverse events

The incidence of AEs is described in Section 10.6.

10.4.2.1.3 Safety hematology

Safety hematology by visit is provided in Table 10-18.

There were no meaningful changes over time in the mean values for hematology parameters of platelets, white blood cell count, neutrophil count, lymphocyte count, monocyte count, eosinophil count, and basophil count in the course of the study (Visit 1 to Visit 7).

Table 10-18 Hematology by visit (Safety analysis set)

		Binocrit/Epoetin alfa HEXAL (N=2497)			
Parameters	**Visits**	**n**	**Mean (std)**	**N implausible[a]**	**Nmiss**
Platelets (10^9/L)	1	2290	222.4 (79.47)	14	193
	2	2082	217.4 (76.48)	4	155
	3	1889	218.3 (75.24)	-	141
	4	1663	213.6 (75.01)	1	133
	5	1510	214.0 (74.36)	-	122
	6	1353	213.8 (71.99)	-	115

		Binocrit/Epoetin alfa HEXAL (N=2497)			
Parameters	**Visits**	**n**	**Mean (std)**	**N implausible[a]**	**Nmiss**
	7	1252	213.8 (74.95)	-	103
White blood cell count (10^9/L)	1	2307	7.562 (14.1943)	11	179
	2	2107	7.159 (2.2464)	3	131
	3	1927	7.204 (2.2201)	-	103
	4	1692	7.128 (2.4228)	1	104
	5	1521	7.162 (2.1730)	-	111
	6	1376	7.129 (2.4142)	-	92
	7	1263	7.088 (2.2289)	-	92
Neutrophil count (10^9/L)	1	1270	4.571 (1.7620)	12	1215
	2	1118	4.650 (2.7480)	2	1121
	3	970	4.720 (1.8795)	-	1060
	4	839	4.613 (2.0833)	1	957
	5	785	4.613 (1.7512)	-	847
	6	670	4.621 (1.9221)	-	798
	7	631	4.573 (1.8059)	-	724
Lymphocyte count (10^9/L)	1	1400	1.624 (0.8806)	11	1086
	2	1254	1.630 (0.7550)	2	985
	3	1100	1.608 (0.6890)	-	930
	4	954	1.585 (0.6718)	1	842
	5	895	1.598 (0.6559)	-	737
	6	778	1.595 (1.0870)	-	690
	7	733	1.596 (0.9246)	-	622
Monocyte count(10^9/L)	1	1280	0.565 (0.2483)	11	1206
	2	1140	0.574 (0.2872)	2	1099
	3	993	0.572 (0.2299)	-	1037
	4	854	0.568 (0.2608)	1	942
	5	799	0.573 (0.2248)	-	833
	6	682	0.572 (0.2335)	-	786
	7	634	0.572 (0.2300)	-	721
Eosinophil count (10^9/L)	1	1193	0.356 (2.9659)	8	1296
	2	1055	0.274 (0.9504)	1	1185
	3	916	0.236 (0.1883)	-	1114
	4	804	0.264 (0.7244)	-	993
	5	755	0.248 (0.2165)	-	877
	6	650	0.234 (0.1959)	-	818
	7	614	0.236 (0.1951)	-	741

		Binocrit/Epoetin alfa HEXAL (N=2497)			
Parameters	**Visits**	**n**	**Mean (std)**	**N implausible[a]**	**Nmiss**
Basophil count (10^9/L)	1	1178	0.373 (4.2182)	-	1319
	2	1040	0.128 (2.2558)	-	1201
	3	898	0.041 (0.0486)	-	1132
	4	785	0.042 (0.0458)	-	1012
	5	739	0.043 (0.0473)	-	893
	6	639	0.041 (0.0420)	-	829
	7	608	0.043 (0.0413)	-	747

- = Not applicable
a. Laboratory values are considered implausible if they are out of the ranges as defined in the SAP. Implausible values are excluded from all other statistics including "n".
Source: Table 4.3.1, Listing 3.3, and Listing 3.4

10.4.2.2 Patients discontinuing the study prematurely and reasons for discontinuations

The number of patients discontinuing the study prematurely and reasons for discontinuations are described in detail in Section 10.1.2.

10.4.2.3 Effectiveness evaluation

10.4.2.3.1 Red blood hematology parameters over time: hemoglobin concentration, red blood cells, reticulocyte counts, hematocrit

Red blood hematology for patients by visit is provided in Table 10-19.

The mean values for hemoglobin, erythrocytes, absolute reticulocytes count, relative reticulocytes count, and hematocrit remained stable (Visit 1 to Visit 7).

Table 10-19 Red blood hematology by visit (Safety analysis set)

		Binocrit/Epoetin alfa HEXAL (N=2497)			
Parameters	**Visits**	**n**	**Mean (std)**	**N implausible[a]**	**Nmiss**
Hemoglobin (g/dL)	1	2381	10.66 (1.352)	10	106
	2	2175	11.17 (1.418)	10	56
	3	1968	11.11 (1.354)	9	53
	4	1733	11.12 (1.389)	7	57
	5	1572	11.18 (1.334)	3	57
	6	1417	11.19 (1.302)	1	50
	7	1304	11.16 (1.299)	3	48
Erythrocytes (10^{12}/L)	1	2258	3.63 (0.570)	1	238
	2	2064	3.79 (0.616)	-	177
	3	1879	3.75 (0.601)	1	150

		Binocrit/Epoetin alfa HEXAL (N=2497)			
Parameters	**Visits**	**n**	**Mean (std)**	**N implausible[a]**	**Nmiss**
	4	1659	3.72 (0.582)	2	136
	5	1508	3.74 (0.592)	2	122
	6	1353	3.74 (0.591)	-	115
	7	1244	3.73 (0.576)	-	111
Absolute reticulocytes count (10^9/L)	1	246	46.0 (27.73)	1	2250
	2	258	47.0 (30.21)	2	1981
	3	206	50.3 (31.54)	6	1818
	4	180	46.4 (29.45)	-	1617
	5	136	41.9 (26.70)	-	1496
	6	132	46.0 (30.92)	-	1336
	7	115	43.9 (29.59)	-	1240
Relative reticulocytes count (%)	1	261	1.74 (0.761)	3	2233
	2	263	1.70 (0.785)	15	1963
	3	258	1.76 (0.903)	1	1771
	4	215	1.74 (0.697)	-	1582
	5	160	1.70 (0.810)	-	1472
	6	143	1.81 (0.912)	-	1325
	7	127	1.83 (0.937)	-	1228
Hematocrit (%)	1	2319	33.0 (4.25)	2	176
	2	2111	34.4 (4.58)	4	126
	3	1920	34.2 (4.32)	-	110
	4	1687	34.2 (4.50)	-	110
	5	1534	34.3 (4.34)	-	98
	6	1376	34.4 (4.21)	-	92
	7	1267	34.3 (4.24)	-	88

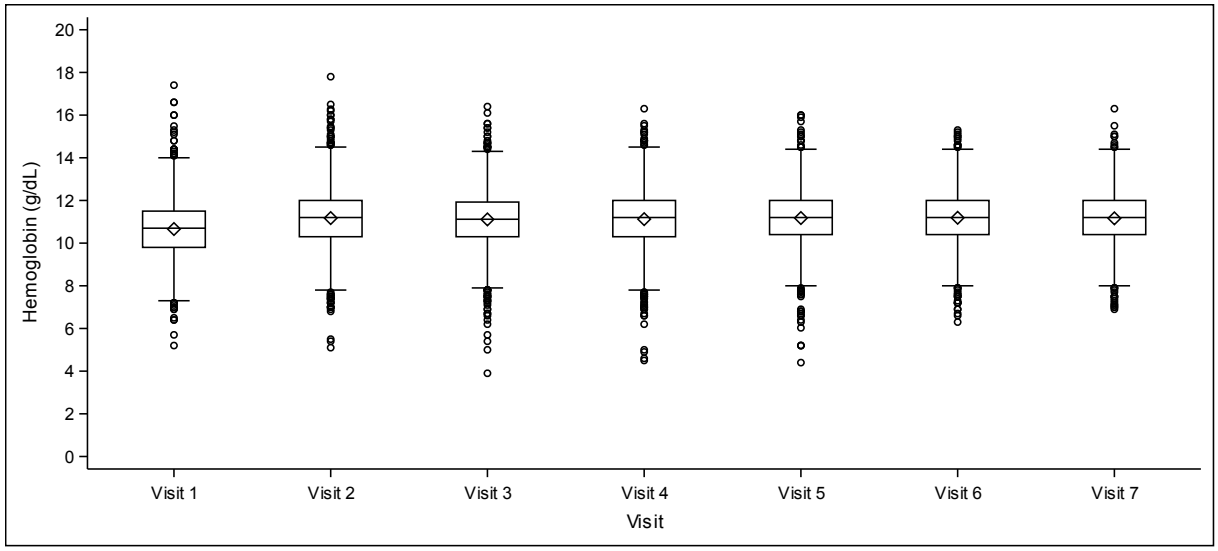
- = Not applicable
a. Laboratory values are considered implausible if they are out of the ranges as defined in the SAP. Implausible values are excluded from all other statistics including “n”.
Source: Table 2.1.1, Listing 3.1, Listing 3.2, and Listing 3.3

A box plot for red blood hematology (including outliers) is provided in Figure 10-2.

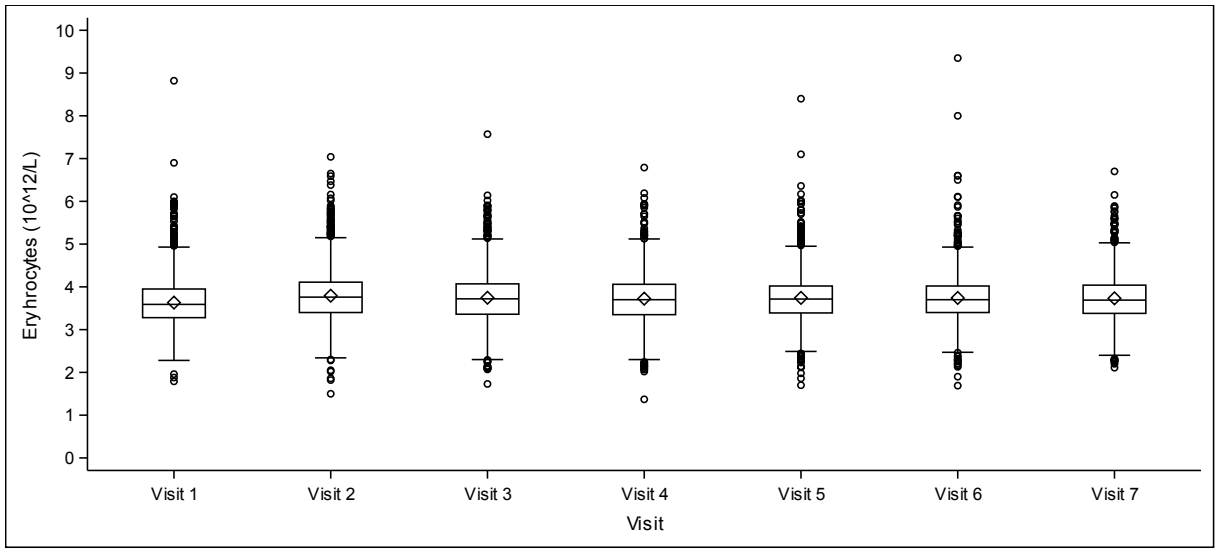
Red blood hematology parameters (hemoglobin, erythrocytes, absolute reticulocytes count, relative reticulocytes count, and hematocrit) remained stable across study visits (data collection time points, approximately every 4 months). Implausible values were excluded from this figure.

Figure 10-2 Box plot: Red blood hematology

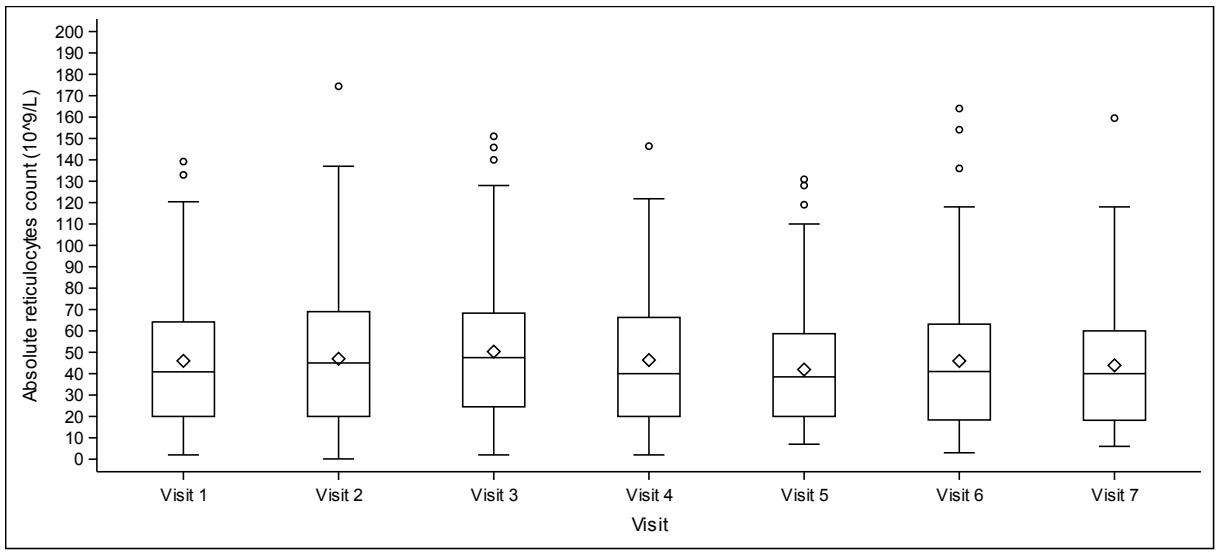
a) Hemoglobin



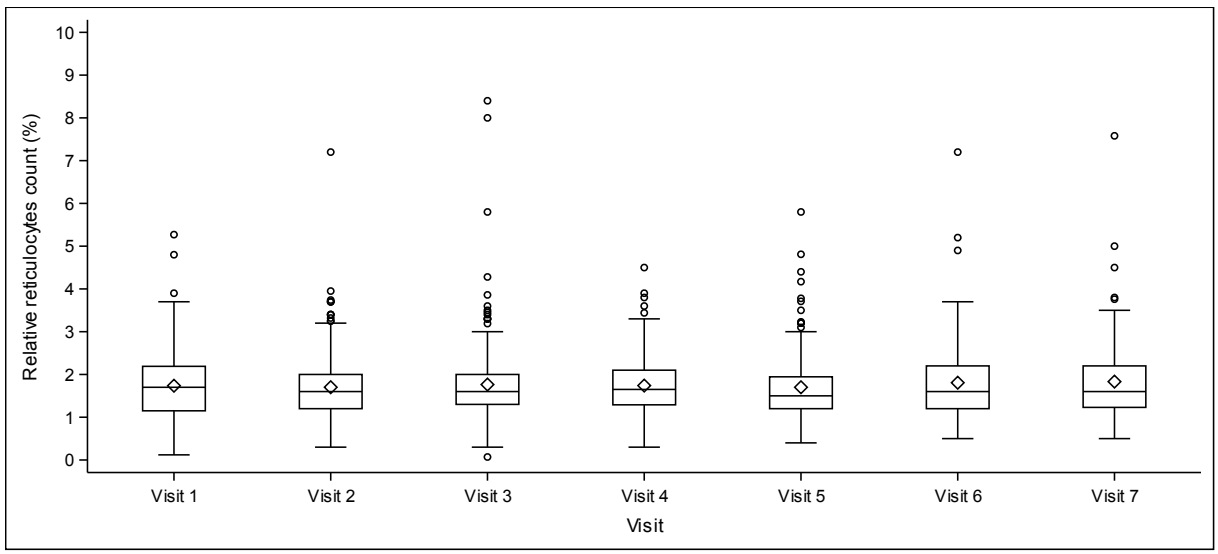
b) Erythrocytes



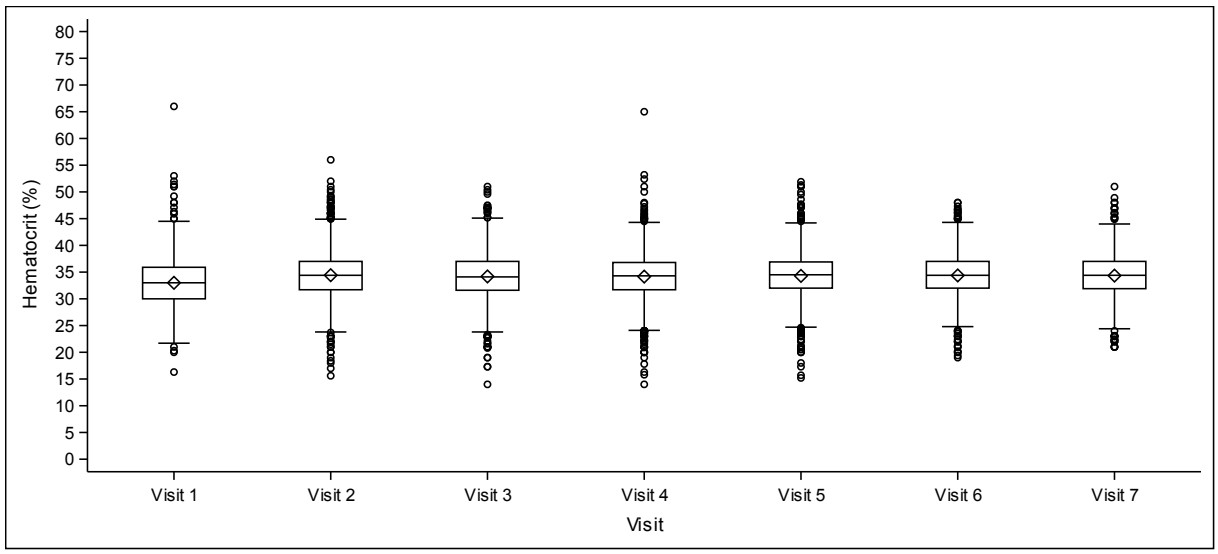
c) Absolute reticulocytes count



d) Relative reticulocytes count



e) Hematocrit



Laboratory values are considered implausible if they are out of the ranges as defined in the SAP. Implausible values are excluded from the figure.
Note: Diamond symbols represents the mean value. Circle symbols above or below the whiskers represent individual outlier values.
Outliers are those observations that fall beyond the whiskers as follows: > (Third Quartile + 1.5 * Interquartile Range) or < (First Quartile – 1.5 * Interquartile Range).
Source: Figure 1.1

Hemoglobin levels within target range (10.0–12.0 g/dL) by visits for patients are provided in Table 10-20.

From Visit 3 onwards, the hemoglobin levels were within the target range for approximately 60% of the patients. Also, more than 56% of the patients had even hemoglobin levels above the target range (>12.0 g/dL).

Table 10-20 Hemoglobin levels within target range (10.0–12.0 g/dL) by visit (Safety analysis set)

Time point Within target range [n (%)][a] Criteria [n (%)][b]	Binocrit/Epoetin alfa HEXAL (N=2497)
Overall[c]	2470
Yes	411 (16.6)
No	2059 (83.4)
Visit 1	2391
Yes	1357 (56.8)
No	1034 (43.2)
Below target range (<10.0 g/dL)	700 (67.7)
Above target range (>12.0 g/dL)	334 (32.3)
Visit 2	2185
Yes	1256 (57.5)
No	929 (42.5)

Below target range (<10.0 g/dL)	387 (41.7)
Above target range (>12.0 g/dL)	542 (58.3)
Visit 3	1977
Yes	1195 (60.4)
No	782 (39.6)
Below target range (<10.0 g/dL)	344 (44.0)
Above target range (>12.0 g/dL)	438 (56.0)
Visit 4	1740
Yes	1031 (59.3)
No	709 (40.7)
Below target range (<10.0 g/dL)	310 (43.7)
Above target range (>12.0 g/dL)	399 (56.3)
Visit 5	1575
Yes	952 (60.4)
No	623 (39.6)
Below target range (<10.0 g/dL)	250 (40.1)
Above target range (>12.0 g/dL)	373 (59.9)
Visit 6	1418
Yes	872 (61.5)
No	546 (38.5)
Below target range (<10.0 g/dL)	224 (41.0)
Above target range (>12.0 g/dL)	322 (59.0)
Visit 7	1307
Yes	803 (61.4)
No	504 (38.6)
Below target range (<10.0 g/dL)	212 (42.1)
Above target range (>12.0 g/dL)	292 (57.9)

a. Percentages are based on the number of patients with hemoglobin data at each visit.
b. Percentages are based on the number of patients with hemoglobin data 'No' within target range at each visit.
c. A patient is considered within target range overall if all non-missing values during the study are within range.
Source: Table 2.1.2

10.4.2.3.2 Iron status over time

Iron status by visit for patients are provided in Table 10-21.

There was slight improvement in the mean values for ferritin across the study visits (data collection time points every 4 months). The mean transferrin saturation remained stable (Visit 1 to Visit 7).

Table 10-21 Iron status by visit (Safety analysis set)

		Binocrit/Epoetin alfa HEXAL (N=2497)			
Parameters	**Visits**	**n**	**Mean (std)**	**N implausible[a]**	**Nmiss**
Ferritin (ng/mL)	1	1725	295.2 (269.00)	9	763
	2	1335	325.0 (305.82)	8	898
	3	1264	352.4 (314.17)	8	758
	4	1098	350.9 (301.13)	8	691
	5	980	353.5 (294.58)	4	648
	6	919	351.5 (294.39)	8	541
	7	821	362.9 (313.32)	4	530
Transferrin Saturation (%)	1	1071	24.3 (11.64)	4	1422
	2	819	26.0 (12.45)	3	1419
	3	774	26.3 (12.21)	5	1251
	4	713	26.0 (11.40)	2	1082
	5	609	25.2 (10.53)	1	1022
	6	572	25.7 (10.66)	1	895
	7	516	24.9 (11.15)	1	838

a. Laboratory values are considered implausible if they are out of the ranges as defined in the SAP. Implausible values are excluded from all other statistics including “n”.
Source: Table 2.4

10.4.2.4 Number of patients who received transfusions

Number of patients who received transfusion are provided in Table 10-22.

Transfusion data was collected from Visit 2 onwards due to which only 2317 patients were expected to have transfusion data available. The majority of the patients (2167 patients [93.5%]) did not receive any transfusions. Of the 148 patients who received a transfusion, 98.0% received a whole blood or packed RBC.

Table 10-22 Transfusions (Safety analysis set)

	Binocrit/Epoetin alfa HEXAL (N=2497)
Number of patients with expected transfusion information	2317
Number of transfusions per patient[a]	
0	2167 (93.5)
1	87 (3.8)
2	30 (1.3)
3	11 (0.5)
4	11 (0.5)
>4	9 (0.4)

	Binocrit/Epoetin alfa HEXAL (N=2497)
Missing	2
Number of transfusions per patient for patients receiving any transfusions	
n	148
Mean (std)	2.1 (2.55)
Median	1.0
Q1, Q3	1.0, 2.0
Min, Max	1, 27
Type of transfusion[b]	
Whole blood or packed RBC	145 (98.0)
Whole blood	20 (13.5)
Packed RBC	128 (86.5)
Other	3 (2.0)
Missing	2
Reason for transfusion[b]	
Worsening of anemia	77 (52.0)
Blood loss not due to chronic kidney disease	47 (31.8)
Other	43 (29.1)
Missing	2

Information on transfusions was only collected from Visit 2.
a. Percentages are based on number of patients with expected transfusion information.
b. Percentages are based on number of patients receiving any transfusions.
Note: A patient may have more than one type or reason for transfusion.
Source: Table 2.2 and Listing 4.1

10.4.3 Other data

10.4.3.1 Dialysis

The number of patients who underwent dialysis by visit are provided in Table 10-23.

A total of 1090 patients (43.7%) were on any type of dialysis at the time of Visit 1; most of these patients (959 [88.0%]) were on hemodialysis. Less than 4% of the patients started on dialysis after entering the study.

Table 10-23 Dialysis (Safety analysis set)

Time point Dialysis [n (%)]	Binocrit/Epoetin alfa HEXAL (N=2497)
Number of patients on dialysis at Visit 1[a]	1090 (43.7)
Hemodialysis[b]	959 (88.0)
Peritoneal dialysis[b]	131 (12.0)

Time point Dialysis [n (%)]	Binocrit/Epoetin alfa HEXAL (N=2497)
Number of patients who first started dialysis during the study[a]	82 (3.3)

a. Percentages are based on the number of patients in the safety analysis set.
b. Percentages are based on the number of patients on dialysis at Visit 1.
Source: Table 4.4.1 and Listing 6.1

10.4.3.2 Immunogenicity

Samples from 2 patients were tested for the presence of anti-epoetin antibodies/ADAs (one at the local laboratory and the other at Hexal AG's central laboratory) and both of which were negative (Table 10-24). The assay method used for the sample assessed at the local laboratory was immunoblot and a radioimmunoprecipitation assay method was performed. for the sample assessed by Hexal AG's central laboratory for which the bioanalytical report is available upon request as per Annex 1. A narrative description of the reported data on these two patients is provided below:

The patient PPD underwent anti-epoetin antibody testing due to decreased hemoglobin on Day 115 (PPD) after receiving s.c. HX575 for approximately 4 months. Hemoglobin, ferritin, and transferrin levels for the patient were 8.3 g/dL (decrease of 2.5 g/dL; 10.8 g/dL at previous visit [Visit 1]), 487 ng/mL, and 19%, respectively. Assessments for reticulocytopenia and bone marrow biopsy were not performed. Since the ADA test result was negative, anti-epoetin antibody induced PRCA was ruled out. Decreased hemoglobin was resolved on Day 213 (PPD) and was considered not related to s.c HX575. The frequency of iron supplementation was increased from every month to every second week. No action was taken with s.c. HX575-507 and the patient continued in the study.

The patient PPD underwent anti-epoetin antibody testing on Day 690 (PPD) after worsening of renal anemia (a reason for ADA testing was not recorded). At this point, the patient had been on s.c. HX575 for at least 2 years. The patient had fluctuating hemoglobin and ferritin levels; hemoglobin at Visit 5: 5.2 g/dL, Visit 6: 7.6 g/dL, and Visit 7: 7.1 g/dL; ferritin levels at Visit 5, Visit 6, and Visit 7 were 46.7 ng/mL, 6.7 ng/mL and 32.0, respectively. Transferrin levels were not available. Since the ADA test result was negative, anti-epoetin antibody induced PRCA was ruled out. The frequency of iron supplementation was decreased from every week to as needed. No action was taken with s.c. HX575-507 and the patient continued in the study.

Table 10-24 Antibody assessment

Patient ID/ Age/Gender	Collection date (Day)	Laboratory details	Result of anti-epoetin antibody assay
PPD	PPD (115)	Other Local Associated Laboratory	NEGATIVE
PPD	PPD (690)	Hexal AG	NEGATIVE

10.5 Other analyses

A sensitivity analysis was performed using data from EDC (the primary source) and safety database (the secondary source) to derive the incidence and IRs and which were included as a separate overall AEs tabulation. Overall, AEs were reported in 1300 patients (3391 events) based on the combined data from the EDC and safety database. There were 2 additional AEs in the combined data from the EDC and safety database (Table 10-26) versus the EDC alone (Table 10-25).

A sensitivity analysis was also performed to account for AEs reported in the EDC by patients with unsigned CRFs (i.e., who did not have PI signatures before DBL). A separate AE summary table was included for FSAF (Table 10-27) and a separate listing provided the AEs reported by those patients with unsigned CRFs. There was 1 patient with an unsigned CRF, but for whom no AEs were reported.

10.6 Adverse events and adverse reactions

10.6.1 Overall summary of adverse events

A summary AE data including AEs, related AEs, AESIs, SAEs, AEs leading to death, AEs leading to s.c. HX575 adjustment/temporary interruption, and AEs leading to s.c. HX575 discontinuation are provided in Table 10-25 for the SAF.

Overall AEs were reported with an IR (per 1000 patient years) of 482 (95% CI: 456, 509); Mild AEs were reported with a highest IR of 214 (95% CI: 198, 231) compared to moderate (157 [95% CI: 144, 171]) or severe (176 [95% CI: 163, 191]) AEs; related AEs with an IR of 7 (95% CI: 5, 11); AESIs with an IR of 126 (95% CI: 115, 139); SAEs with an IR of 279 (95% CI: 261, 298); deaths with an IR of 132 (95% CI: 121, 144); AEs leading to s.c. HX575 adjustment/temporary interruption with an IR of 23 (95% CI: 19, 29); and AEs leading to s.c. HX575 discontinuation with an IR of 24 (95% CI: 19, 29).

Table 10-25 Overall summary of adverse events (Safety analysis set)

	Binocrit/Epoetin alfa HEXAL (N=2497)			
Adverse event category	**n**	**E**	**% (95% Clopper-Pearson CI)**	**IR (95% CI)**
Any AE	1300	3389	52.1 (50.1, 54.0)	482 (456, 509)
Mild AE	648	1193	26.0 (24.2, 27.7)	214 (198, 231)
Moderate AE	512	1087	20.5 (18.9, 22.1)	157 (144, 171)
Severe AE	617	1109	24.7 (23.0, 26.5)	176 (163, 191)
Related AE	27	30	1.1 (0.7, 1.6)	7 (5, 11)
Mild related AE	17	17	0.7 (0.4, 1.1)	5 (3, 7)
Moderate related AE	9	9	0.4 (0.2, 0.7)	2 (1, 5)
Severe related AE	3	4	0.1 (<0.1, 0.4)	1 (<1, 3)
Any AE of special interest	429	614	17.2 (15.7, 18.7)	126 (115, 139)
Related AE of special interest	15	18	0.6 (0.3, 1.0)	4 (2, 7)
SAE of special interest	328	441	13.1 (11.8, 14.5)	94 (84, 104)
Related SAE of special interest	6	8	0.2 (0.1, 0.5)	2 (1, 4)
Any SAE	893	2011	35.8 (33.9, 37.7)	279 (261, 298)

	Binocrit/Epoetin alfa HEXAL (N=2497)			
Adverse event category	**n**	**E**	**% (95% Clopper-Pearson CI)**	**IR (95% CI)**
Related SAE	7	9	0.3 (0.1, 0.6)	2 (1, 4)
AE leading to death	483	731	19.3 (17.8, 20.9)	132 (121, 144)
Related AE leading to death	3	4	0.1 (<0.1, 0.4)	1 (<1, 3)
SAE leading to death	483	731	19.3 (17.8, 20.9)	132 (121, 144)
Related SAE leading to death	3	4	0.1 (<0.1, 0.4)	1 (<1, 3)
AE leading to study drug adjustment/temporary interruption	85	124	3.4 (2.7, 4.2)	23 (19, 29)
AE leading to study drug discontinuation	88	110	3.5 (2.8, 4.3)	24 (19, 29)
Related AE leading to study drug discontinuation	8	8	0.3 (0.1, 0.6)	2 (1, 4)
SAE leading to study drug discontinuation	72	93	2.9 (2.3, 3.6)	20 (16, 25)
Related SAE leading to study drug discontinuation	0	0	0.0 (0.0, 0.1)	NC (NC, NC)

n = Number of patients; E = Number of events; IR = Incidence Rate per 1000 patient years; NC = Not Calculable.Note: For each category, patients are included only once, even if they experienced multiple events in that category.
Incidence rate was calculated using a Poisson distribution model with the number of patients with events in each AE category offset by the sum of patient years for all patients. Patient years was calculated as the sum of duration of risk ([date of the AE or end of study date [if no AE occurred] – informed consent date + 1]/365.25) for each patient.
Source: Table 3.1.1, Listing 2.5, and Listing 2.6

Overall AEs captured in the safety database are provided in Table 10-26.

Table 10-26 Overall adverse events including adverse events captured in a safety database (Safety analysis set)

	Binocrit/Epoetin alfa HEXAL (N=2497)			
Adverse event category	**n**	**E**	**% (95% Clopper-Pearson CI)**	**IR (95% CI)**
Any AE	1300	3391	52.1 (50.1, 54.0)	482 (456, 509)
Related AE	27	30	1.1 (0.7, 1.6)	7 (5, 11)
Any AE of special interest	429	614	17.2 (15.7, 18.7)	126 (115, 139)
Related AE of special interest	15	18	0.6 (0.3, 1.0)	4 (2, 7)
SAE of special interest	328	441	13.1 (11.8, 14.5)	94 (84, 104)
Related SAE of special interest	6	8	0.2 (0.1, 0.5)	2 (1, 4)
Any SAE	893	2013	35.8 (33.9, 37.7)	279 (261, 298)
Related SAE	7	9	0.3 (0.1, 0.6)	2 (1, 4)
AE leading to death	483	731	19.3 (17.8, 20.9)	132 (121, 144)
Related AE leading to death	3	4	0.1 (<0.1, 0.4)	1 (<1, 3)
SAE leading to death	483	731	19.3 (17.8, 20.9)	132 (121, 144)
Related SAE leading to death	3	4	0.1 (<0.1, 0.4)	1 (<1, 3)

n = Number of patients; E = Number of events; IR = Incidence Rate per 1000 patient years; NC = Not Calculable.

	Binocrit/Epoetin alfa HEXAL (N=2497)			
Adverse event category	**n**	**E**	**% (95% Clopper-Pearson CI)**	**IR (95% CI)**

Note: This table includes AEs that were captured by study's primary source (i.e., EDC) and secondary source (i.e., safety database) as described in the SAP.
For each category, patients are included only once, even if they experienced multiple events in that category.
Incidence rate was calculated using a Poisson distribution model with the number of patients with events in each AE category offset by the sum of patient years for all patients. Patient years was calculated as the sum of duration of risk ([date of the AE or end of study date [if no AE occurred] – informed consent date + 1]/365.25) for each patient.
Source: Table 3.1.2 and Listing 2.5

A summary of AE data including AEs, related AEs, AEs of special interest, SAEs, AEs leading to death, AEs leading to s.c. HX575 adjustment/temporary interruption, and AEs leading to s.c. HX575 discontinuation are provided in Table 10-27 for the FSAF which included patients with unsigned CRFs.

Table 10-27 Overall adverse events including patients with unsigned case report forms (Full safety analysis set)

	Binocrit/Epoetin alfa HEXAL (N=2498)			
Adverse event category	**n**	**E**	**% (95% Clopper-Pearson CI)**	**IR (95% CI)**
Any AE	1300	3389	52.0 (50.1, 54.0)	482 (456, 509)
Mild AE	648	1193	25.9 (24.2, 27.7)	214 (198, 231)
Moderate AE	512	1087	20.5 (18.9, 22.1)	157 (144, 171)
Severe AE	617	1109	24.7 (23.0, 26.4)	176 (163, 191)
Related AE	27	30	1.1 (0.7, 1.6)	7 (5, 11)
Mild related AE	17	17	0.7 (0.4, 1.1)	5 (3, 7)
Moderate related AE	9	9	0.4 (0.2, 0.7)	2 (1, 5)
Severe related AE	3	4	0.1 (<0.1, 0.4)	1 (<1, 3)
Any AE of special interest	429	614	17.2 (15.7, 18.7)	126(115, 139)
Related AE of special interest	15	18	0.6 (0.3, 1.0)	4 (2, 7)
SAE of special interest	328	441	13.1 (11.8, 14.5)	94 (84, 104)
Related SAE of special interest	6	8	0.2 (0.1, 0.5)	2 (1, 4)
Any SAE	893	2011	35.7 (33.9, 37.7)	279 (261, 298)
Related SAE	7	9	0.3 (0.1, 0.6)	2 (1, 4)
AE leading to death	483	731	19.3 (17.8, 20.9)	132(121, 144)
Related AE leading to death	3	4	0.1 (<0.1, 0.4)	1 (<1, 3)
SAE leading to death	483	731	19.3 (17.8, 20.9)	132(121, 144)
Related SAE leading to death	3	4	0.1 (<0.1, 0.4)	1 (<1, 3)
AE leading to study drug adjustment/temporary interruption	85	124	3.4 (2.7, 4.2)	23 (19, 29)
AE leading to study drug discontinuation	88	110	3.5 (2.8, 4.3)	24 (19, 29)
Related AE leading to study drug discontinuation	8	8	0.3 (0.1, 0.6)	2 (1, 4)
SAE leading to study drug discontinuation	72	93	2.9 (2.3, 3.6)	20 (16, 25)

Adverse event category	Binocrit/Epoetin alfa HEXAL (N=2498)			
	n	E	% (95% Clopper-Pearson CI)	IR (95% CI)
Related SAE leading to study drug discontinuation	0	0	0.0 (0.0, 0.1)	NC (NC, NC)

n = Number of patients; E = Number of events; IR = Incidence Rate per 1000 patient years; NC = Not Calculable.
Patient PPD was the only patient who had Unsigned CRFs, however no AEs were documented during the study.
Note: For each category, patients are included only once, even if they experienced multiple events in that category.
Incidence rate was calculated using a Poisson distribution model with the number of patients with events in each AE category offset by the sum of patient years for all patients. Patient years was calculated as the sum of duration of risk ([date of the AE or end of study date [if no AE occurred] – informed consent date + 1]/365.25) for each patient.
Source: Table 3.1.3, Listing 2.5.1, and Listing 2.5.2

10.6.2 Adverse events of special interest (AESIs)

The incidence of AESIs (primary endpoint) is described in Section 10.4.1.1.

The incidence of serious AESI is described in Section 10.4.1.2.

The incidence of AESIs related to s.c. HX575 is described in Section 10.4.1.3.

The incidence of serious AESI related to s.c. HX575 is described in Section 10.4.1.4.

10.6.3 Serious adverse events

SAEs and SAEs related to s.c. HX575 are summarized below.

10.6.3.1 Any serious adverse events (secondary endpoint)

The incidences of SAEs that occurred in ≥1% of patients by SOC and PT are provided in Table 10-28.

SAEs were reported in 893 patients (35.8% [95% CI: 33.9, 37.7]), with an IR (per 1000 patient years) of 279 (95% CI: 261, 298).

The most frequently reported SAEs by SOC were infections and infestations with an IR (per 1000 patient years) of 79 (95% CI: 70, 88); general disorders and administration site conditions with an IR of 64 (95% CI: 56, 73); and cardiac disorders with an IR of 65 (95% CI: 57, 74).

The most frequently reported SAEs by PT were death (with no reported reason) with an IR (per 1000 patient years) of 34 (95% CI: 29, 41); pneumonia with an IR of 19 (95% CI: 15, 24); and cardiac failure with an IR of 18 (95% CI: 14, 22).

Table 10-28 Serious adverse events regardless of study drug relationship by system organ class and preferred term that occurred in ≥1% of patients (Safety analysis set)

System organ class *Preferred term*	Binocrit/Epoetin alfa HEXAL (N=2497)			
	n	E	% (95% Clopper-Pearson CI)	IR (95% CI)
Any serious adverse events	893	2011	35.8 (33.9, 37.7)	279 (261, 298)
Infections and infestations	279	398	11.2 (10.0, 12.5)	79 (70, 88)
Pneumonia	68	74	2.7 (2.1, 3.4)	19 (15, 24)
Sepsis	51	52	2.0 (1.5, 2.7)	14 (11, 18)
COVID-19	26	26	1.0 (0.7, 1.5)	7 (5, 10)
General disorders and administration site conditions	233	258	9.3 (8.2, 10.5)	64 (56, 73)
Death	126	126	5.0 (4.2, 6.0)	34 (29, 41)
Cardiac disorders	232	307	9.3 (8.2, 10.5)	65 (57, 74)
Cardiac failure	64	76	2.6 (2.0, 3.3)	18 (14, 22)
Cardiac failure acute	29	30	1.2 (0.8, 1.7)	8 (5, 11)
Gastrointestinal disorders	103	147	4.1 (3.4, 5.0)	29 (24, 35)
Injury, poisoning and procedural complications	99	157	4.0 (3.2, 4.8)	27 (23, 33)
Fall	24	24	1.0 (0.6, 1.4)	7 (4, 10)
Renal and urinary disorders	95	117	3.8 (3.1, 4.6)	26 (21, 32)
Acute kidney injury	29	31	1.2 (0.8, 1.7)	8 (5, 11)
Respiratory, thoracic and mediastinal disorders	90	122	3.6 (2.9, 4.4)	25 (20, 30)
Dyspnoea	28	35	1.1 (0.7, 1.6)	8 (5, 11)
Nervous system disorders	74	91	3.0 (2.3, 3.7)	20 (16, 26)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	68	93	2.7 (2.1, 3.4)	19 (15, 24)
Vascular disorders	62	73	2.5 (1.9, 3.2)	17 (13, 22)
Metabolism and nutrition disorders	60	64	2.4 (1.8, 3.1)	16 (13, 21)
Blood and lymphatic system disorders	56	76	2.2 (1.7, 2.9)	15 (12, 20)
Anaemia	40	50	1.6 (1.1, 2.2)	11 (8, 15)

n = Number of patients; E = Number of events; IR = Incidence Rate per 1000 patient years.
Note: Adverse events were coded using MedDRA version 25.1. For each system organ class and preferred term, patients are included only once, even if they experienced multiple events in that system organ class or preferred term.
Incidence rate was calculated using a Poisson distribution model with the number of patients with each AE offset by the sum of patient years for all patients. Patient years was calculated as the sum of duration of risk ([date of the AE or end of study date [if no AE occurred] - informed consent date + 1]/365.25) for each patient.
Source: Table 3.3.2 and Listing 2.2

10.6.3.2 Serious adverse events related to study drug

SAEs related to s.c. HX575 by SOC and PT are provided in Table 10-29.

Related SAEs were reported in 7 patients (0.3% [95% CI: 0.1, 0.6]), with an IR (per 1000 patient years) of 2 (95% CI: 1, 4).

The most frequently reported SAEs by SOC were vascular disorders in 3 patients (0.1% [95% CI: <0.1, 0.4]) with an IR of 1 (95% CI: <1, 3); and nervous system disorders in 2 patients (0.1% [95% CI: <0.1, 0.3]) with an IR of 1 (95% CI: <1, 2). The remaining SAEs occurred in 1 patient (<0.1% [95% CI: <0.1, 0.2]).

The most frequently reported SAEs by PT was hypertension in 2 patients (0.1% [95% CI: <0.1, 0.3)]). The IR (per 1000 patient years) was 1 (95% CI: <1, 2). The remaining SAEs by PT had an IR of <1 (95% CI: (<1, 2).

Table 10-29 Serious related adverse events by system organ class and preferred term (Safety analysis set)

System organ class *Preferred term*	Binocrit/Epoetin alfa HEXAL (N=2497)			
	n	E	% (95% Clopper-Pearson CI)	IR (95% CI)
Any serious treatment-related adverse events	7	9	0.3 (0.1, 0.6)	2 (1, 4)
Vascular disorders	3	3	0.1 (<0.1, 0.4)	1 (<1, 3)
Hypertension	2	2	0.1 (<0.1, 0.3)	1 (<1, 2)
Hypertensive crisis	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Nervous system disorders	2	2	0.1 (<0.1, 0.3)	1 (<1, 2)
Cerebral ischaemia	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Haemorrhage intracranial	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Blood and lymphatic system disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Anaemia	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Cardiac disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Cardiac failure	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Breast neoplasm	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Respiratory, thoracic and mediastinal disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Pulmonary embolism	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)

n = Number of patients; E = Number of events; IR = Incidence Rate per 1000 patient years.
Note: Adverse events were coded using MedDRA version 25.1. For each system organ class and preferred term, patients are included only once, even if they experienced multiple events in that system organ class or preferred term.
Incidence rate was calculated using a Poisson distribution model with the number of patients with each AE offset by the sum of patient years for all patients. Patient years was calculated as the sum of duration of risk ([date of the AE or end of study date [if no AE occurred] – informed consent date + 1]/365.25) for each patient.
Source: Table 3.3.3 and Listing 2.2

10.6.4 Adverse events

Related AEs, AEs by intensity, AEs related to s.c. HX575 and by intensity are summarized below. Refer to Section 10.6.5.1 and Section 10.6.5.2 details of the AEs/related AEs leading to s.c. HX575 discontinuation and Section 10.6.6.1 and Section 10.6.6.2 for details of the AEs/related AEs leading to death.

10.6.4.1 Any adverse event

AEs (≥1%) by SOC and PT are provided in Table 10-30.

AEs were reported in 1300 patients (52.1% [95% CI: 50.1, 54.0]), with an IR (per 1000 patient years) of 482 (95% CI: 456, 509).

The most frequently reported AEs by SOC were infections and infestations with an IR (per 1000 patient years) of 127 (95% CI: 116, 140); general disorders and administration site conditions with an IR of 88 (95% CI: 79, 98); and cardiac disorders with an IR of 74 (95% CI: 65, 83).

The most frequently reported AEs by PT were death (with no reported reason) with an IR (per 1000 patient years) of 34 (95% CI: 29, 41); pneumonia with an IR of 20 (95% CI: 16, 25); anemia with an IR of 19 (95% CI: 15, 24); and COVID-19 and hyperkalemia with an IR of 19 (95% CI: 15, 24).

Table 10-30 Adverse events regardless of study drug relationship that occurred in ≥1% of patients by system organ class and preferred term (Safety analysis set)

System organ class *Preferred term*	Binocrit/Epoetin alfa HEXAL (N=2497)			
	n	E	% (95% Clopper-Pearson CI)	IR (95% CI)
Any adverse events	1300	3389	52.1 (50.1, 54.0)	482 (456, 509)
Infections and infestations	431	644	17.3 (15.8, 18.8)	127 (116, 140)
Pneumonia	73	81	2.9 (2.3, 3.7)	20 (16, 25)
COVID-19	68	69	2.7 (2.1, 3.4)	19 (15, 24)
Urinary tract infection	59	78	2.4 (1.8, 3.0)	16 (13, 21)
Sepsis	52	53	2.1 (1.6, 2.7)	14 (11, 19)
General disorders and administration site conditions	313	362	12.5 (11.3, 13.9)	88 (79, 98)
Death	126	126	5.0 (4.2, 6.0)	34 (29, 41)
Pyrexia	31	38	1.2 (0.8, 1.8)	8 (6, 12)
Oedema peripheral	25	27	1.0 (0.6, 1.5)	7 (5, 10)
Cardiac disorders	263	356	10.5 (9.4, 11.8)	74 (65, 83)
Cardiac failure	66	79	2.6 (2.0, 3.4)	18 (14, 23)
Cardiac failure acute	29	30	1.2 (0.8, 1.7)	8 (5, 11)
Atrial fibrillation	26	26	1.0 (0.7, 1.5)	7 (5, 10)
Gastrointestinal disorders	184	271	7.4 (6.4, 8.5)	52 (45, 60)
Diarrhoea	40	42	1.6 (1.1, 2.2)	11 (8, 15)
Gastrointestinal haemorrhage	25	27	1.0 (0.6, 1.5)	7 (5, 10)

System organ class *Preferred term*	Binocrit/Epoetin alfa HEXAL (N=2497)			
	n	E	% (95% Clopper-Pearson CI)	IR (95% CI)
Injury, poisoning and procedural complications	163	255	6.5 (5.6, 7.6)	46 (39, 54)
Fall	36	38	1.4 (1.0, 2.0)	10 (7, 14)
Metabolism and nutrition disorders	155	186	6.2 (5.3, 7.2)	44 (37, 51)
Hyperkalaemia	68	80	2.7 (2.1, 3.4)	19 (15, 24)
Nervous system disorders	142	173	5.7 (4.8, 6.7)	40 (34, 47)
Headache	24	27	1.0 (0.6, 1.4)	7 (4, 10)
Renal and urinary disorders	135	165	5.4 (4.6, 6.4)	37 (32, 44)
Acute kidney injury	33	35	1.3 (0.9, 1.9)	9 (6, 13)
Chronic kidney disease	27	28	1.1 (0.7, 1.6)	7 (5, 11)
Renal impairment	26	28	1.0 (0.7, 1.5)	7 (5, 10)
Respiratory, thoracic and mediastinal disorders	131	184	5.2 (4.4, 6.2)	36 (31, 43)
Dyspnoea	39	49	1.6 (1.1, 2.1)	11 (8, 15)
Vascular disorders	124	151	5.0 (4.1, 5.9)	35 (29, 41)
Hypertension	35	38	1.4 (1.0, 1.9)	10 (7, 13)
Blood and lymphatic system disorders	101	127	4.0 (3.3, 4.9)	28 (23, 34)
Anaemia	69	83	2.8 (2.2, 3.5)	19 (15, 24)
Musculoskeletal and connective tissue disorders	97	114	3.9 (3.2, 4.7)	27 (22, 33)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	79	111	3.2 (2.5, 3.9)	22 (17, 27)
Investigations	76	97	3.0 (2.4, 3.8)	21 (17, 26)
Skin and subcutaneous tissue disorders	57	69	2.3 (1.7, 2.9)	16 (12, 20)

n = Number of patients; E = Number of events; IR = Incidence Rate per 1000 patient years.
Note: Adverse events were coded using MedDRA version 25.1. For each system organ class and preferred term, patients are included only once, even if they experienced multiple events in that system organ class or preferred term.
Incidence rate was calculated using a Poisson distribution model with the number of patients with each AE offset by the sum of patient years for all patients. Patient years was calculated as the sum of duration of risk ([date of the AE or end of study date [if no AE occurred] - informed consent date + 1]/365.25) for each patient.
Source: Table 3.3.1 and Listing 2.5

10.6.4.2 Adverse events related to study drug

AEs with a suspected causal relationship to s.c. HX575 by SOC and PT are provided in Table 10-31.

Related AEs were reported in 27 patients (1.1% [95% CI: 0.7, 1.6]), with an IR (per 1000 patient years) of 7 (95% CI: 5, 11).

The most frequently reported AEs by SOC were vascular disorders with an IR (per 1000 patient years) of 2 (95% CI: 1, 4) and skin and subcutaneous tissue disorders with an IR of 1 (95% CI: <1, 3).

The most frequently reported AE by PT was hypertension with an IR (per 1000 patient years) of 2 (95% CI: 1, 4).

Table 10-31 Adverse events with a suspected relationship to study drug by system organ class and preferred term (Safety analysis set)

	Binocrit/Epoetin alfa HEXAL (N=2497)			
System organ class *Preferred term*	**n**	**E**	**% (95% Clopper-Pearson CI)**	**IR (95% CI)**
Any adverse events	27	30	1.1 (0.7, 1.6)	7 (5, 11)
Vascular disorders	8	8	0.3 (0.1, 0.6)	2 (1, 4)
Hypertension	6	6	0.2 (0.1, 0.5)	2 (1, 4)
Accelerated hypertension	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Hypertensive crisis	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Skin and subcutaneous tissue disorders	4	4	0.2 (<0.1, 0.4)	1 (<1, 3)
Rash	3	3	0.1 (<0.1, 0.4)	1 (<1, 3)
Drug reaction with eosinophilia and systemic symptoms	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Blood and lymphatic system disorders	3	3	0.1 (<0.1, 0.4)	1 (<1, 3)
Anaemia	2	2	0.1 (<0.1, 0.3)	1 (<1, 2)
Haemoglobinaemia	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Nervous system disorders	3	3	0.1 (<0.1, 0.4)	1 (<1, 3)
Cerebral ischaemia	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Haemorrhage intracranial	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Hypoaesthesia	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Respiratory, thoracic and mediastinal disorders	2	2	0.1 (<0.1, 0.3)	1 (<1, 2)
Epistaxis	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Pulmonary embolism	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Injury, poisoning and procedural complications	1	2	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Arteriovenous graft thrombosis	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Vascular graft thrombosis	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Cardiac disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Cardiac failure	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Gastrointestinal disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Diarrhoea	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Immune system disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Hypersensitivity	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)

System organ class *Preferred term*	Binocrit/Epoetin alfa HEXAL (N=2497)			
	n	E	% (95% Clopper-Pearson CI)	IR (95% CI)
Investigations	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Haemoglobin increased	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Metabolism and nutrition disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Hyperkalaemia	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Musculoskeletal and connective tissue disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Arthralgia	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Breast neoplasm	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Psychiatric disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Insomnia	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)

n = Number of patients; E = Number of events; IR = Incidence Rate per 1000 patient years.
Note: Adverse events were coded using MedDRA version 25.1. For each system organ class and preferred term, patients are included only once, even if they experienced multiple events in that system organ class or preferred term.
Incidence rate was calculated using a Poisson distribution model with the number of patients with each AE offset by the sum of patient years for all patients. Patient years was calculated as the sum of duration of risk ([date of the AE or end of study date [if no AE occurred] - informed consent date + 1]/365.25) for each patient.
Source: Table 3.3.4 and Listing 2.5

10.6.4.3 Adverse events by intensity

Adverse events (≥1%) by intensity (mild, moderate, and severe), SOC, and PT are provided in Table 10-32.

Severe AEs were reported in 617 patients (24.7% [95% CI: 23.0, 26.5]), with an IR (per 1000 patient years) of 176 (95% CI: 163, 191).

The most frequently reported severe AEs by SOC were general disorders and administration site conditions with an IR (per 1000 patient years) of 57 (95% CI: 50, 65); infections and infestations with an IR of 46 (95% CI: 40, 54); and cardiac disorders with an IR of 45 (95% CI: 38, 52).

The most frequently reported severe AEs by PT were death (with no reported reason) with an IR (per 1000 patient years) of 34 (95% CI: 29, 41); sepsis with an IR of 13 (95% CI: 10, 17); pneumonia with an IR of 11 (95% CI: 8, 15); and cardiac failure with an IR of 11 (95% CI: 8, 15).

Table 10-32 Adverse events that occurred in ≥1% of patients by system organ class and preferred term (Safety analysis set)

System organ class *Preferred term*	Binocrit/Epoetin alfa HEXAL (N=2497)			
	n	E	% (95% Clopper-Pearson CI)	IR (95% CI)
Any adverse events-mild	648	1193	26.0 (24.2, 27.7)	214 (198, 231)
Infections and infestations	187	239	7.5 (6.5, 8.6)	53 (46, 62)
Urinary tract infection	42	54	1.7 (1.2, 2.3)	12 (9, 16)
COVID-19	42	43	1.7 (1.2, 2.3)	12 (9, 16)
Metabolism and nutrition disorders	94	112	3.8 (3.1, 4.6)	26 (21, 32)
Hyperkalaemia	45	55	1.8 (1.3, 2.4)	12 (9, 17)
General disorders and administration site conditions	87	98	3.5 (2.8, 4.3)	24 (20, 30)
Gastrointestinal disorders	83	103	3.3 (2.7, 4.1)	23 (19, 28)
Injury, poisoning and procedural complications	66	99	2.6 (2.0, 3.4)	18 (14, 23)
Nervous system disorders	64	71	2.6 (2.0, 3.3)	18 (14, 23)
Musculoskeletal and connective tissue disorders	63	69	2.5 (1.9, 3.2)	17 (14, 22)
Vascular disorders	51	58	2.0 (1.5, 2.7)	14 (11, 18)
Investigations	46	62	1.8 (1.4, 2.4)	13 (9, 17)
Respiratory, thoracic and mediastinal disorders	44	55	1.8 (1.3, 2.4)	12 (9, 16)
Cardiac disorders	39	43	1.6 (1.1, 2.1)	11 (8, 15)
Blood and lymphatic system disorders	39	42	1.6 (1.1, 2.1)	11 (8, 15)
Anaemia	26	28	1.0 (0.7, 1.5)	7 (5, 10)
Renal and urinary disorders	32	35	1.3 (0.9, 1.8)	9 (6, 12)
Skin and subcutaneous tissue disorders	31	38	1.2 (0.8, 1.8)	8 (6, 12)
Any adverse events-moderate	512	1087	20.5 (18.9, 22.1)	157 (144, 171)
Infections and infestations	138	175	5.5 (4.7, 6.5)	39 (33, 46)
Pneumonia	29	30	1.2 (0.8, 1.7)	8 (6, 11)
Cardiac disorders	89	113	3.6 (2.9, 4.4)	25 (20, 30)
Cardiac failure	27	34	1.1 (0.7, 1.6)	7 (5, 11)
Injury, poisoning and procedural complications	82	118	3.3 (2.6, 4.1)	23 (18, 28)
Gastrointestinal disorders	76	104	3.0 (2.4, 3.8)	21 (17, 26)
Renal and urinary disorders	65	75	2.6 (2.0, 3.3)	18 (14, 23)
Vascular disorders	57	69	2.3 (1.7, 2.9)	16 (12, 20)
Blood and lymphatic system disorders	50	61	2.0 (1.5, 2.6)	14 (10, 18)
Anaemia	34	41	1.4 (0.9, 1.9)	9 (7, 13)

System organ class *Preferred term*	Binocrit/Epoetin alfa HEXAL (N=2497)			
	n	E	% (95% Clopper-Pearson CI)	IR (95% CI)
Respiratory, thoracic and mediastinal disorders	47	60	1.9 (1.4, 2.5)	13 (10, 17)
Metabolism and nutrition disorders	45	49	1.8 (1.3, 2.4)	12 (9, 17)
Nervous system disorders	36	45	1.4 (1.0, 2.0)	10 (7, 14)
General disorders and administration site conditions	36	44	1.4 (1.0, 2.0)	10 (7, 14)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	34	40	1.4 (0.9, 1.9)	9 (7, 13)
Musculoskeletal and connective tissue disorders	32	39	1.3 (0.9, 1.8)	9 (6, 12)
Investigations	29	32	1.2 (0.8, 1.7)	8 (6, 11)
Any adverse events-severe	617	1109	24.7 (23.0, 26.5)	176 (163, 191)
General disorders and administration site conditions	209	220	8.4 (7.3, 9.5)	57 (50, 65)
Death	126	126	5.0 (4.2, 6.0)	34 (29, 41)
Infections and infestations	169	230	6.8 (5.8, 7.8)	46 (40, 54)
Sepsis	48	49	1.9 (1.4, 2.5)	13 (10, 17)
Pneumonia	40	44	1.6 (1.1, 2.2)	11 (8, 15)
Cardiac disorders	163	200	6.5 (5.6, 7.6)	45 (38, 52)
Cardiac failure	39	42	1.6 (1.1, 2.1)	11 (8, 15)
Cardiac failure acute	27	27	1.1 (0.7, 1.6)	7 (5, 11)
Respiratory, thoracic and mediastinal disorders	56	69	2.2 (1.7, 2.9)	15 (12, 20)
Gastrointestinal disorders	49	64	2.0 (1.5, 2.6)	13 (10, 18)
Nervous system disorders	47	57	1.9 (1.4, 2.5)	13 (10, 17)
Renal and urinary disorders	44	55	1.8 (1.3, 2.4)	12 (9, 16)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	38	53	1.5 (1.1, 2.1)	10 (8, 14)
Injury, poisoning and procedural complications	33	38	1.3 (0.9, 1.9)	9 (6, 13)
Metabolism and nutrition disorders	25	25	1.0 (0.6, 1.5)	7 (5, 10)

n = Number of patients; E = Number of events; IR = Incidence Rate per 1000 patient years.
Note: Adverse events were coded using MedDRA version 25.1. For each system organ class and preferred term, patients are included only once, even if they experienced multiple events in that system organ class or preferred term.
Incidence rate was calculated using a Poisson distribution model with the number of patients with each AE offset by the sum of patient years for all patients. Patient years was calculated as the sum of duration of risk ([date of the AE or end of study date [if no AE occurred] - informed consent date + 1]/365.25) for each patient.
Source: Table 3.3.5 and Listing 2.5

10.6.4.4 Adverse events related to study drug and by intensity

AEs related to s.c. HX575 by intensity (mild, moderate, and severe), SOC, and PT are provided in Table 10-33.

Related severe AEs were reported in 3 patients (0.1% [95% CI: <0.1, 0.4]), with an IR (per 1000 patient years) of 1 (95% CI: <1, 3).

Severe AEs by SOC were nervous system disorders with an IR (per 1000 patient years) of 1 (95% CI: <1, 2); and cardiac disorders and respiratory, thoracic and mediastinal disorders with an IR of <1 (95% CI: <1, 2).

severe AEs by PT were cerebral ischemia, hemorrhage intracranial, cardiac failure, and pulmonary embolism with an IR (per 1000 patient years) of <1 (95% CI: <1, 2).

Table 10-33 Adverse events related to study drug by intensity, system organ class and preferred term (Safety analysis set)

System organ class *Preferred term*	Binocrit/Epoetin alfa HEXAL (N=2497)			
	n	E	% (95% Clopper-Pearson CI)	IR (95% CI)
Any treatment-related adverse events (mild)	17	17	0.7 (0.4, 1.1)	5 (3, 7)
Vascular disorders	7	7	0.3 (0.1, 0.6)	2 (1, 4)
Hypertension	5	5	0.2 (0.1, 0.5)	1 (1, 3)
Accelerated hypertension	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Hypertensive crisis	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Blood and lymphatic system disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Haemoglobinaemia	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Gastrointestinal disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Diarrhoea	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Immune system disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Hypersensitivity	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Injury, poisoning and procedural complications	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Vascular graft thrombosis	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Investigations	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Haemoglobin increased	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Metabolism and nutrition disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Hyperkalaemia	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Musculoskeletal and connective tissue disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Arthralgia	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Nervous system disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Hypoaesthesia	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Respiratory, thoracic and mediastinal disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)

System organ class *Preferred term*	n	Binocrit/Epoetin alfa HEXAL (N=2497) E	% (95% Clopper-Pearson CI)	IR (95% CI)
Epistaxis	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Skin and subcutaneous tissue disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Rash	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Any treatment-related adverse events (moderate)	9	9	0.4 (0.2, 0.7)	2 (1, 5)
Skin and subcutaneous tissue disorders	3	3	0.1 (<0.1, 0.4)	1 (<1, 3)
Rash	2	2	0.1 (<0.1, 0.3)	1 (<1, 2)
Drug reaction with eosinophilia and systemic symptoms	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Blood and lymphatic system disorders	2	2	0.1 (<0.1, 0.3)	1 (<1, 2)
Anaemia	2	2	0.1 (<0.1, 0.3)	1 (<1, 2)
Injury, poisoning and procedural complications	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Arteriovenous graft thrombosis	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Breast neoplasm	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Psychiatric disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Insomnia	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Vascular disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Hypertension	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Any treatment-related adverse events (severe)	3	4	0.1 (<0.1, 0.4)	1 (<1, 3)
Nervous system disorders	2	2	0.1 (<0.1, 0.3)	1 (<1, 2)
Cerebral ischaemia	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Haemorrhage intracranial	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Cardiac disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Cardiac failure	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Respiratory, thoracic and mediastinal disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Pulmonary embolism	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)

n = Number of patients; E = Number of events; IR = Incidence Rate per 1000 patient years.
Note: Adverse events were coded using MedDRA version 25.1. For each system organ class and preferred term, patients are included only once, even if they experienced multiple events in that system organ class or preferred term.
Incidence rate was calculated using a Poisson distribution model with the number of patients with each AE offset by the sum of patient years for all patients. Patient years was calculated as the sum of duration of risk ([date of the AE or end of study date [if no AE occurred] – informed consent date + 1]/365.25) for each patient.

System organ class *Preferred term*	n	Binocrit/Epoetin alfa HEXAL (N=2497) E	% (95% Clopper-Pearson CI)	IR (95% CI)

Source: Table 3.3.6 and Listing 2.5

10.6.5 Adverse events leading to study drug discontinuation

Data by patient for AEs leading to s.c. HX575 discontinuation are presented below.

10.6.5.1 Any adverse events leading to study drug discontinuation

AEs leading to s.c. HX575 discontinuation by SOC are provided in Table 10-34.

AEs leading to s.c. HX575 discontinuation were reported in 88 patients (3.5% [95% CI: 2.8, 4.3]), with an IR (per 1000 patient years) of 24 (95% CI: 19, 29).

The most frequently reported AE leading to s.c. HX575 discontinuation by SOC was cardiac disorders with an IR (per 1000 patient years) of 7 (95% CI: 4, 10).

There were no AEs leading to s.c. HX575 discontinuation by PT per ≥1% cut-off criteria.

High-grade B-cell lymphoma, colon cancer, metastases to lung, papillary renal cell carcinoma were the events which were malignant in nature and reported under the SOC of neoplasms benign, malignant and unspecified (incl cysts and polyps). All these events were not suspected as related to s.c. HX575.

Table 10-34 Adverse events leading to study drug discontinuation by system organ class (Safety analysis set)

System organ class	Binocrit/Epoetin alfa HEXAL (N=2497)			
	n	E	% (95% Clopper-Pearson CI)	IR (95% CI)
Any adverse events leading to study drug discontinuation	88	110	3.5 (2.8, 4.3)	24 (19, 29)
Cardiac disorders	24	27	1.0 (0.6, 1.4)	7 (4, 10)
General disorders and administration site conditions	16	16	0.6 (0.4, 1.0)	4 (3, 7)
Nervous system disorders	13	14	0.5 (0.3, 0.9)	4 (2, 6)
Respiratory, thoracic and mediastinal disorders	11	12	0.4 (0.2, 0.8)	3 (2, 5)
Infections and infestations	10	11	0.4 (0.2, 0.7)	3 (1, 5)
Renal and urinary disorders	8	8	0.3 (0.1, 0.6)	2 (1, 4)
Gastrointestinal disorders	6	6	0.2 (0.1, 0.5)	2 (1, 4)
Skin and subcutaneous tissue disorders	4	4	0.2 (<0.1, 0.4)	1 (<1, 3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	4	0.1 (<0.1, 0.4)	1 (<1, 3)
Blood and lymphatic system disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Hepatobiliary disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)

System organ class	Binocrit/Epoetin alfa HEXAL (N=2497)			
	n	E	% (95% Clopper-Pearson CI)	IR (95% CI)
Immune system disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Injury, poisoning and procedural complications	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Metabolism and nutrition disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Product issues	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Psychiatric disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)
Vascular disorders	1	1	<0.1 (<0.1, 0.2)	<1 (<1, 2)

n = Number of patients; E = Number of events; IR = Incidence Rate per 1000 patient years.
Note: Adverse events were coded using MedDRA version 25.1. For each system organ class and preferred term, patients are included only once, even if they experienced multiple events in that system organ class or preferred term.
Incidence rate was calculated using a Poisson distribution model with the number of patients with each AE offset by the sum of patient years for all patients. Patient years was calculated as the sum of duration of risk ([date of the AE or end of study date [if no AE occurred] - informed consent date + 1]/365.25) for each patient.
Source: Table 3.3.7 and Listing 2.3

10.6.5.2 Related adverse events leading to study drug discontinuation

Related AEs leading to discontinuation by time in study until the event, PT, action taken, and outcome are provided in Table 10-35.

Related AEs leading to s.c. HX575 discontinuation were reported in 8 patients (0.3% [95% CI: 0.1, 0.6]), with an IR (per 1000 patient years) of 2 (95% CI: 1, 4).

Table 10-35 Related adverse events leading to study drug discontinuation

Patient ID/Age/Gender	Days in study until AE[a]	Preferred term	Action taken[b]	Outcome
PPD	-	Rash	2	Not recovered/Not resolved
PPD	14	Drug reaction with eosinophilia and systemic symptoms	2	Recovered/Resolved
PPD	26	Rash	2,3	Recovered/Resolved
PPD	4	Hypoaesthesia	2	Recovered/Resolved
PPD	173	Diarrhoea	2	Recovered/Resolved
PPD	256	Hypertension	2	Recovered/Resolved
PPD	384	Insomnia	2	Not recovered/Not resolved
PPD	-	Hypersensitivity	2	Recovered/Resolved

- = Not applicable
a. Days in Study until AE is only calculated for complete AE start dates.
b. Action Taken with Study Drug: 1 = Drug of interest dose adjusted/temporarily interrupted; 2 = Drug of interest permanently discontinued due to this AE; 3 = Adverse Event treatment medication introduced or adjusted; 4 = Non-drug therapy given; 5 = Other.
Source: Listing 2.5

SAEs leading to s.c. HX575 discontinuation were reported in 72 patients (2.9% [95% CI: 2.3, 3.6]), with an IR (per 1000 patient years) of 20 (95% CI: 16, 25) (Table 10-25).

None of the patients experienced related SAEs leading to s.c. HX575 discontinuation.

10.6.6 Adverse events leading to death

10.6.6.1 Any adverse events leading to death

AEs leading to death (≥1%) by SOC and PT are provided in Table 10-36.

AEs leading to death were reported in 483 patients (19.3% [95% CI: 17.8, 20.9]), with an IR (per 1000 patient years) of 132 (95% CI: 121, 144) within the study duration. However, there were 5 patients (6 events) who died after dropping out of the study.

The most frequently reported AEs leading to death by SOC were general disorders and administration site conditions with an IR (per 1000 patient years) of 51 (95% CI: 44, 59); infections and infestations with an IR of 35 (95% CI: 30, 42); and cardiac disorders with an IR of 32 (95% CI: 27, 38).

The most frequently reported AEs leading to death by PT were death (with no reported reason) with an IR (per 1000 patient years) of 34 (95% CI: 29, 41); sepsis with an IR of 12 (95% CI: 9, 16); and pneumonia with an IR of 9 (95% CI: 7, 13).

Table 10-36 Adverse events leading to death by system organ class and preferred term that occurred in ≥1% of patients (Safety analysis set)

System organ class *Preferred term*	Binocrit/Epoetin alfa HEXAL (N=2497)			
	n	E	% (95% Clopper-Pearson CI)	IR (95% CI)
Any adverse events leading to death	483	731	19.3 (17.8, 20.9)	132 (121, 144)
General disorders and administration site conditions	188	197	7.5 (6.5, 8.6)	51 (44, 59)
Death	126	126	5.0 (4.2, 6.0)	34 (29, 41)
Infections and infestations	129	159	5.2 (4.3, 6.1)	35 (30, 42)
Sepsis	43	44	1.7 (1.2, 2.3)	12 (9, 16)
Pneumonia	34	34	1.4 (0.9, 1.9)	9 (7, 13)
Cardiac disorders	118	137	4.7 (3.9, 5.6)	32 (27, 38)
Cardiac failure	28	28	1.1 (0.7, 1.6)	8 (5, 11)
Cardiac failure acute	25	25	1.0 (0.6, 1.5)	7 (5, 10)
Respiratory, thoracic and mediastinal disorders	38	47	1.5 (1.1, 2.1)	10 (8, 14)
Nervous system disorders	36	42	1.4 (1.0, 2.0)	10 (7, 14)
Renal and urinary disorders	26	30	1.0 (0.7, 1.5)	7 (5, 10)

n = Number of patients; E = Number of events; IR = Incidence Rate per 1000 patient years.
Note: Adverse events were coded using MedDRA version 25.1. For each system organ class and preferred term, patients are included only once, even if they experienced multiple events in that system organ class or preferred term.

System organ class *Preferred term*	n	Binocrit/Epoetin alfa HEXAL (N=2497) E	% (95% Clopper-Pearson CI)	IR (95% CI)

Incidence rate was calculated using a Poisson distribution model with the number of patients with each AE offset by the sum of patient years for all patients. Patient years was calculated as the sum of duration of risk ([date of the AE or end of study date [if no AE occurred] – informed consent date + 1]/365.25) for each patient.
Source: Table 3.3.8 and Listing 2.1

10.6.6.2 Related adverse events leading to death

AEs with a suspected causal relationship to HX575-507 leading to death by time in study until the event, PT, action taken, and outcome are provided in Table 10-37.

Related AEs leading to death were reported in 3 patients (0.1% [95% CI: (<0.1, 0.4]), with an IR (per 1000 patient years) of 1 (95% CI: <1, 3) (Table 10-25).

Table 10-37 Related adverse events leading to death

Patient ID/Age/Gender	Days in study until AE[a]	Preferred term	Action taken[b]	Outcome
PPD /PPD/	132	Cerebral ischaemia	-	Fatal
PPD /PPD/	684	Haemorrhage intracranial	-	Fatal
PPD /PPD/	105	Cardiac failure	3,4	Fatal
	105	Pulmonary embolism	3,4	Fatal

- = Not applicable
a. Days in Study until AE is only calculated for complete AE start dates.
b. Action Taken with Study Drug: 1 = Drug of interest dose adjusted/temporarily interrupted; 2 = Drug of interest permanently discontinued due to this AE; 3 = Adverse Event treatment medication introduced or adjusted; 4 = Non-drug therapy given; 5 = Other.
Source: Listing 2.5

10.6.7 COVID-19-related adverse events

Overall, 99 patients experienced COVID-19 related AEs during the study. Of these, 36 AEs were reported in 28 patients which lead to death (fatal outcome) and 74 AEs were reported in 71 patients which were not fatal.

10.6.8 Pregnancy reporting leading to maternal exposure during pregnancy

Patient PPD, a PPD-year-old female received 49.6 IU/kg of epoetin alfa once every week subcutaneously for 1.89 years. Current medical conditions included PPD, PPD and PPD. Previous obstetric history included pregnancy PPD PPD baby born by PPD. Concomitant medications included PPD, sodium bicarbonate, PPD PPD, indapamide, PPD and torasemide. In PPD, an event of maternal exposure during pregnancy was reported. It was reported that patient gave a birth to a normal PPD child via PPD in pregnancy week 36+4. APGAR scores at 1 min were 6, at 5 mins was 8, and at 10 mins was 10; head circumference was 32.5 cm.

11 Discussion

The purpose of this NI-PASS was to increase the dataset on the safe use of s.c. HX575 by extending the safety database of the product in patients with CKD-induced anemia, who received s.c. HX575 treatment and by monitoring closely the AE profile under real-life post-approval conditions.

This study was conducted in 10 European countries (Bulgaria, Croatia, Germany, Greece, Italy, Poland, Romania, Slovakia, Slovenia, and Spain) and enrolled 2510 eligible patients. Overall, 2497 patients (99.5%) received s.c. HX575 and were included in the SAF: 1334 patients (53.1%) completed the study and 1176 patients (46.9%) were discontinued from the study as per investigator decision. The majority of patients were recruited at sites in Germany, Italy, Bulgaria, or Greece.

At baseline, approximately half (52.5%) of the patients had Stage 5 CKD and less than half of the patients were on dialysis (1090 patients [43.7%]). Approximately one quarter of patients had at least one relevant medical history condition and almost all patients had at least one current (ongoing) medical history condition.

The overall monitored time of patient exposure to s.c. HX575 was 3600.2 years; the median treatment duration was 1.82 years.

The key results of this study included incidence of relevant and expected rare AEs, general safety, tolerability, and effectiveness of s.c. HX575 treatment in patients with CKD-induced anemia are discussed in detail in below Section 11.1.

11.1 Key results

11.1.1 Relevant and expected rare AEs (defined as AESI)

The primary endpoint of this study was the incidence of AESIs (AESI including LOE and PRCA).

No patient experienced PRCA.

LOE was reported in 1 patient, 7 days after patient's start in the study while on s.c. HX575 treatment for approximately 7 months. During the time when LOE was reported, the patient was suffering from gastric hemorrhage which resulted in blood loss and anemia (decrease in hemoglobin). The investigator did not collect blood for ADA assessment. The event resolved in PPD (at an unrecorded date). After a short interruption of s.c. HX575, the patient resumed study treatment and completed the study.

The Sponsor's medical experts did not consider this as a confirmed LOE case, as the cause of the decrease in hemoglobin values was due to foregoing blood loss. Moreover, after interruption, HX575 treatment was resumed and was effective for the remainder of study.

The most frequently reported AESIs were major thromboembolic and cardiovascular events in 6.5% of patients with an IR (per 1000 patient years) of 46 (95% CI: 39, 53), congestive heart failure in 4.8% of patients with an IR of 33 (95% CI: 27, 39), and hypertension (worsening or newly developing hypertension, hypertensive crisis, uncontrolled hypertension) in 2.0% of patients with an IR of 13 (95% CI: 10, 18).

AESIs with a suspected causal relationship to s.c. HX575 (cerebral ischemia, hemorrhage intracranial, cardiac failure) led to death in 3 patients. One patient with related AESI of breast neoplasm recovered after surgical removal of the tumor. In 1 patient, a related AESI of drug reaction with eosinophilia and systemic symptoms recovered after treatment discontinuation.

11.1.2 Assessment of general safety, tolerability, and effectiveness

The secondary endpoints assessed in this study were incidence of SAEs, AEs, number of patients discontinuing the study prematurely and reasons for discontinuations, red blood hematology parameters over time, number of patients who received transfusions during study, and weekly epoetin dosage over time.

Overall, SAEs were reported in 893 patients (35.8%) with an IR (per 1000 patient years) of 279 (95% CI: 261, 298). The most frequently reported SAEs by PT were death (with no reported reason) with an IR (per 1000 patient years) of 34 (95% CI: 29, 41); pneumonia with an IR of 19 (95% CI: 15, 24); and cardiac failure with an IR of 18 (95% CI: 14, 22).

The most frequently reported related SAEs by PT was hypertension in 2 patients (0.1% [95% CI: <0.1, 0.3]). The IR (per 1000 patient years) was 1 (95% CI: <1, 2). The remaining SAEs by PT had an IR of <1 (95% CI: (<1, 2).

Overall, AEs were reported in 1300 patients (52.1%) with an IR (per 1000 patient years) of 482 (95% CI: 456, 509). Mild AEs were reported with a highest IR of 214 (95% CI: 198, 231) compared to moderate (157 [95% CI: 144, 171]) or severe (176 [95% CI: 163, 191]) AEs. Most frequently reported AEs by PTs were death (with no reported reason) with an IR (per 1000 patient years) of 34 (95% CI: 29, 41); pneumonia with an IR of 20 (95% CI: 16, 25); anemia with an IR of 19 (95% CI: 15, 24); and COVID-19 and hyperkalemia with an IR of 19 (95% CI: 15, 24).. The most frequently reported AEs by PT related to s.c. HX575 was hypertension with an IR (per 1000 patient years) of 2 (95% CI: 1, 4). Considering the infectious nature of COVID-19, novel origin (no human immunity) and the pandemic situation, there is no causal role of epoetin alfa suspected for COVID-19 infection.

In total, 483 (19.3%) deaths were reported in the study. The most frequently reported AEs leading to death (by PTs) were death (with no reported reason) with an IR (per 1000 patient years) of 34 (95% CI: 29, 41); sepsis with an IR of 12 (95% CI: 9, 16); and pneumonia with an IR of 9 (95% CI: 7, 13). Related AEs leading to death were reported in 3 patients (0.1% [95% CI: (<0.1, 0.4]), with an IR (per 1000 patient years) of 1 (95% CI: <1, 3).

Overall, 88 patients (3.5% [95% CI: 2.8, 4.3]) reported any AEs leading to discontinuation of s.c. HX575 treatment which were in the SOC of cardiac disorder with an IR (per 1000 patient years) of 7 (95% CI: 4, 10). SAEs leading to s.c. HX575 discontinuation were reported in 72 patients (2.9% [95% CI: 2.3, 3.6]) with an IR (per 1000 patient years) of 20 (95% CI: 16, 25).

Overall, red blood hematology parameters (hemoglobin concentration, RBC, absolute and relative reticulocyte counts, and hematocrit) over time remained stable (Visit 1 to Visit 7) in all the patients. Target hemoglobin levels (10 g/dL to 12 g/dL) were achieved and maintained during Visit 1 to Visit 7 (as specified in SmPC reference) and hematocrit levels were in the target range (30% to 36% per SmPC) in all the patients.

Of the 2317 patients where transfusion information was planned to be collected; 2167 (93.5%) patients did not receive any transfusions during study due to reduced need for transfusion by Epoetin alfa treatment.

The other secondary endpoints assessed as specified in the SAP were other hematology parameters over time (platelets, WBC, neutrophils, lymphocytes, monocytes, eosinophils and basophils), iron status (ferritin and transferrin) over time, iron supplementation, and weekly epoetin dosage over time. No meaningful differences in the mean values of other hematology parameters by visits (Visit 1 to Visit 7) were observed in the study. Whereas, there was slight improvement in the mean values for ferritin across the study visits (data collection time points every 4 months) and the mean transferrin saturation remained stable (Visit 1 to Visit 7). More than half of the patients (1740 [69.7%]) received iron supplementation during the study.

Mean (std) weekly epoetin dosage received by patients ranged from 99.12 (84.063) IU/kg at Visit 1 to 94.24 (84.405) IU/kg at Visit 7 which was within the range as specified in the SmPC.

The ADA results for 2 patients who were tested for the presence of anti-epoetin antibodies were negative.

11.2 Limitations

One of the limitations of the study was related to COVID-19 pandemic during the study period, wherein onsite visits were postponed due to local constricts and site calls were also cancelled due to the increased workload of the site staff. This might have been a reason for some patients not completing the 24 months observation period.

In this open-label study, only patients treated with s.c. HX575 were included and there were no comparison groups of either untreated patients or patients treated with other ESAs.

11.3 Interpretation

Of the 2497 CKD patients who received s.c. HX575 treatment, there were no reports of PRCA.

LOE was reported in 1 patient, but sponsor's medical experts did not consider this as a confirmed LOE case. In this patient, gastric hemorrhage was the underlying cause for recurrent gastric blood loss which resulted in persistent hemoglobin decrease. The patient was not tested for ADA and no PRCA was suspected. Moreover, s.c. HX575 treatment was resumed after a one-month interruption and remained effective until study completion.

The AESIs defined in the study protocol for Binocrit®/Epoetin alfa HEXAL® treatment were thromboembolic events, hypertension/hypertensive crisis, seizure, premature death, hypersensitivity reactions (including anaphylactic reactions), hyperkalemia, tumor growth potential and congestive heart failure which were included in the study to be assessed as AESIs (as per Binocrit®/Epoetin alfa HEXAL RMP effective at study initiation). The results reported thromboembolic and cardiovascular events with an IR (per 1000 patient years) of 46 (95% CI: 39, 53), congestive heart failure with an IR of 33 (95% CI: 27, 39), and hypertension with an IR of 13 (95% CI: 10, 18).

The related AESIs of cerebral ischemia, hemorrhage intracranial, cardiac failure led to death in 3 patients. These patients had multiple concurrent conditions and concomitant medications which are confounding factors for the event. The other patient reporting related AESI of breast

neoplasm had no known prior history of malignancy and the event resolved after surgical removal of the tumor. In one patient a related AESI of drug reaction with eosinophilia and systemic symptoms recovered after treatment discontinuation. Severe cutaneous adverse reactions have been reported in association with epoetin alfa treatment. Reported IRs and % of AESIs and overall AEs are consistent with frequencies of known ADRs included in the SmPC.

More than half of the patients were at Stage 5 of CKD at enrollment with mean (std) time since diagnosis of 7.05 (7.723) years, population age was quite high with a mean age of 69.7 years. More than 20% of enrolled patient were 80+ years old, with high comorbidity due to severe CKD, and almost all the patients had multiple concurrent medical conditions and several ongoing concomitant medications; all of which likely contributed to the deaths reported in the study. Considering the nature of study (observational) and elderly patient population with significant comorbidities, limited follow-up data might be obtainable, contributing to limited information on causes of death reported in the study.

During the study period, the Binocrit RMP was updated (v18.1 was approved by EMA on 8-Jul-2021) in alignment with the originator RMP update and several safety topics are no longer considered important identified/potential risks as they had been at the time of protocol development. Results of study HX575-507 are consistent with the updated risk profile of Epoetin alfa and no new safety concerns were noted in the study.

The results of the present NI-PASS reconfirm in a real-life setting the safety of s.c. administration of HX575 in the long-term treatment of renal anemia.

11.4 Generalizability

This study covered patients from 10 European countries namely Bulgaria, Croatia, Germany, Greece, Italy, Poland, Romania, Slovakia, Slovenia, and Spain and so the results may be extended to other countries.

Regarding patient selection, the inclusion criteria were minimized to obtain representative overview of CKD-induced anemia with or without dialysis treatment. Thus, the characteristics of the study population are expected to reflect the characteristics of the real-world population in terms of the eligibility criteria that were applied.

In terms of demographics, the study covered both males and females and almost all patients had at least one ongoing relevant medical history condition during the study. From a disease perspective, different primary mechanisms of CKD were included, and major stages of CKD were 3 to 5, wherein approximately half of the patients having Stage 5 CKD. Also, the study included both patients on hemodialysis and peritoneal dialysis. Importantly, the study also covered a quite long range of time since diagnosis of CKD.

Approximately two thirds of the enrolled patients were treatment-naive and one third of the patients had been pretreated with any ESA authorized in the EU.

This population-based cohort study reflects the general CKD patient population who are eligible to receive s.c. HX575 treatment. The large sample size and the real-life setting of this study supports the generalizability of the key study outcome.

12 Other information

Not applicable.

13 Conclusion

This NI-PASS increased the dataset on the safe use of s.c. HX575 treatment of CKD-induced anemia under real-life post-approval conditions, with the primary objective of assessing and monitoring rare AESIs (particularly PRCA). Monitoring a safety analysis set of 2497 patients and covering a total of 3600.2 patient years, the study detected no new safety signals; in particular no PRCA case occurred. The nature and frequencies of the reported AESIs and overall AEs are consistent with those of the known ADRs included in the SmPC.

The study results reconfirmed that the s.c. administration route for HX575 treatment in renal anemia is well-tolerated with no new safety concerns noted in the study. The post-approval commitment that was agreed with EMA in March 2016 has therefore been fulfilled.

14 References

References are available upon request.

Binocrit® RMP, last update approved on 21-Aug-2023. Available from: https://www.ema.europa.eu/en/documents/rmp-summary/binocrit-epar-risk-management-plan-summary_en.pdf (accessed on 5-Sep-2023)

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Boven K, Stryker S, Knight J, et al (2005) The increased incidence of pure red cell aplasia with an Eprex formulation in uncoated rubber stopper syringes. Kidney Int; 67(6):2346-53.

Epoetin alfa HEXAL® RMP, last update approved on 21-Aug-2023. Available from: https://www.ema.europa.eu/en/documents/rmp-summary/epoetin-alfa-hexal-epar-risk-management-plan-summary_.pdf (accessed on 5-Sep-2023)

Epoetin alfa HEXAL® SmPC, last update approved on 21-Aug-2023. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/epoetin-alfa-hexal (accessed on 5-Sep-2023)

Appendices

Annex 1. List of stand-alone documents

The following documents can be provided upon request.

Number	Document reference number	Date	Title
1	List of investigator and study sites and List of Ethic Committees	24-Aug-2023	HX575-507 - Investigator and EC list 24Aug2023
2	Protocol HX575-507 Version 2.0	23-Apr-2018	Multicenter non-interventional post-authorization safety study (NI-PASS) to monitor the incidence of relevant and expected rare adverse events including lack of efficacy among CKD patients receiving s.c. Binocrit® or Epoetin alfa HEXAL®
3	English Master Samples of the written information and ICF versions	14-Oct-2016 04-May-2018	ICF V01.01 ICF V02.02
4	Final Statistical Analysis Plan Version 3.0	31-Jan-2023	Statistical Analysis Plan
5	Post-Lock Tables, Listings and Figures Approval	16-Aug-2023	TFLs
6	Bioanalytical report	17-Oct-2023	Bioanalytical report for ADA

Annex 2. Additional information

None