Clinical trial results:
A phase III, randomized, assessor-blinded, active-controlled, multicenter study of the efficacy and safety of APO-EPO as compared to Procrit® when given subcutaneously to patients with anemia of chronic kidney disease stage 5D who are currently not on epoetin replacement therapy

Summary

EudraCT number	2011-005057-31
Trial protocol	CZ HU SK BG GR RO
Global end of trial date	18 September 2017

Results information

Result version number	v1 (current)
This version publication date	12 September 2021
First version publication date	12 September 2021

Trial information

Trial identification

Sponsor protocol code	APO-EPO-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	APOTEX Inc.
Sponsor organisation address	150 Signet Drive, Toronto, Canada, M9L 1T9
Public contact	Apotex Clinical Operations, APOTEX Inc., clinicalqa@apotex.com
Scientific contact	Apotex Clinical Operations, APOTEX Inc., clinicalqa@apotex.com
Sponsor organisation name	APOTEX Inc.
Sponsor organisation address	150 Signet Drive, Toronto, Canada, M9L 1T9
Public contact	Clincal Operations, APOTEX Inc., clinicalqa@apotex.com
Scientific contact	Clincal Operations, APOTEX Inc., clinicalqa@apotex.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 September 2017
Global end of trial reached?	Yes
Global end of trial date	18 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the therapeutic equivalence of Apotex's epoetin alfa (APO-EPO) versus US registered epoetin alfa (Procrit®) for correction of the hemoglobin (Hb) concentration in patients with anemia of chronic kidney disease (CKD) stage 5 maintained on stable hemodialysis (CKD stage 5D).

Protection of trial subjects:

The study was conducted in accordance with the protocol, principles of Good Clinical Practice (GCP), Declaration of Helsinki and amendments, and applicable local regulations. Independent oversight of study was provided by Data and Safety Monitoring Board, which assessed the accumulating safety data from the study (10 meetings were conducted during study course). All subjects were fully informed of all aspects of clinical study, including its experimental nature, its purpose, the procedures involved, the expected duration, the potential risk and benefits, any discomfort it may entail as well as possibility to discontinue at any time in the local language. Collected protected health information obtained during the study was processed in compliance with the Personal Data Protection laws and legislations governing personal data protection in all countries.

Background therapy:

All patients enrolled in the study were on chronic stable hemodialysis (at least 3 times per week). Iron stores were monitored regularly and maintained using iron replacement therapy as per local practice of the study sites. For patients with low iron store levels (TSAT <20% or ferritin <100 ng/ml) despite iron replacement therapy, i.v. iron sucrose - Venofer® was used. It was provided by the Sponsor within the frame of the Protocol.

Evidence for comparator:

Procrit® is the original recombinant human epoetin alfa compounds, manufactured by Amgen Inc., USA. In clinical studies of CKD patients on dialysis, Procrit® increased hemoglobin levels and decreased the need for RBC transfusion. Overall, more than 95% of patients were RBC transfusion-independent after receiving Procrit® for 3 months. The safety and efficacy of Procrit® were evaluated in 13 clinical studies involving intravenous administration to a total of 1010 anemic patients on dialysis. Overall, more than 90% of the patients experienced improvement in hemoglobin concentrations. The median maintenance dose necessary to maintain the hemoglobin between 10 and 12 g/dl was approximately 75 IU/kg t.i.w. (Procrit US Package Insert, FDA)

Actual start date of recruitment	01 October 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 18
Country: Number of subjects enrolled	Romania: 19

Country: Number of subjects enrolled	Slovakia: 8
Country: Number of subjects enrolled	Bulgaria: 162
Country: Number of subjects enrolled	Czechia: 10
Country: Number of subjects enrolled	Greece: 52
Country: Number of subjects enrolled	Georgia: 39
Country: Number of subjects enrolled	Lebanon: 4
Country: Number of subjects enrolled	Serbia: 93
Country: Number of subjects enrolled	Tunisia: 39
Country: Number of subjects enrolled	Ukraine: 89
Worldwide total number of subjects	533
EEA total number of subjects	269

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	392
From 65 to 84 years	140
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 533 subjects were randomized at 57 study centers in 11 countries (Bulgaria, Czechia, Georgia, Greece, Lebanon, Poland, Romania, Serbia, Slovakia, Tunisia, and Ukraine) between 23 SEP 2013 and 17 OCT 2016. Subjects were randomized in a 2:1 ratio - 355 subjects in the APO-EPO and 178 in the Procrit® group.

Pre-assignment

Screening details:

Patients above 18 years with anemia (hemoglobin level below 10 g/dl) of chronic kidney disease stage 5 who were on stable hemodialysis were enrolled. Patients were not receiving epoetin replacement therapy at enrollment and had sufficient iron stores. During enrollment 482 subjects were considered as screen failures.

Pre-assignment period milestones

Number of subjects started	533
Number of subjects completed	533

Period 1

Period 1 title	Correction phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

The assessor(s) – investigators participating in the patient assessments were blinded to the treatment allocation throughout the study. The allocated treatment was disclosed only to the unblinded study staff, who was responsible for the receipt, accountability, preparation, and administration of the study treatment. The unblinded staff did not communicate to the assessor(s) the medication allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	APO-EPO

Arm description:

APO-EPO as recombinant human epoetin alfa was developed as a proposed biosimilar to the US-registered epoetin alfa Procrit®. The product contains the identical amino acid sequence as an isolated natural EPO. It was administered s.c., t.i.w. and was titrated individually according to the pre-specified rules to achieve stable Hb concentrations

Arm type	Experimental
Investigational medicinal product name	recombinant human epoetin alfa
Investigational medicinal product code	APO-EPO
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details:

Provided as single-dose preservative-free vials containing 2,000, 3,000, 4,000 or 10,000 units of epoetin alfa per milliliter in citrate-buffered formulation.
The starting dose will be 25 IU/kg, administered s.c., t.i.w (i.e. a total dose of 75 IU/kg per week) and will be titrated individually in order to achieve stable Hb concentrations of 10.0-11.0 g/dl.

Arm title	Procrit

Arm description:

Procrit is a recombinant human epoetin alfa, has the same biological effects as endogenous EPO. It was

administered s.c., t.i.w. and was titrated individually according to the pre-specified rules to achieve stable Hb concentrations

Arm type	Active comparator
Investigational medicinal product name	recombinant human epoetin alfa
Investigational medicinal product code	Procrit
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details:

Provided as a single-dose, preservative-free vial. Each 1 ml of solution contains 2,000, 3,000, 4,000,or 10,000 units of epoetin alfa.
The starting dose will be 25 IU/kg, administered s.c., t.i.w (i.e. a total dose of 75 IU/kg per week) and will be titrated individually in order to achieve stable Hb concentrations of 10.0-11.0 g/dl.

Number of subjects in period 1	APO-EPO	Procrit
Started	355	178
Completed	319	166
Not completed	36	12
Adverse event, serious fatal	3	-
Consent withdrawn by subject	11	7
Adverse event, non-fatal	12	2
Need for rescue medication	2	1
Administrative problems	2	1
Lack of efficacy	2	-
Prohibited concomitant medication	2	-
Protocol deviation	1	-
Other not specified	1	1

Period 2

Period 2 title	Maintenance phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

The assessor(s) – investigators participating in the patient assessments were blinded to the treatment allocation throughout the study. The allocated treatment was disclosed only to the unblinded study staff, who was responsible for the receipt, accountability, preparation, and administration of the study treatment. The unblinded staff did not communicate to the assessor(s) the medication allocation.

Arms

Are arms mutually exclusive?	Yes

Arm title	APO-EPO
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	recombinant human epoetin alfa
Investigational medicinal product code	APO-EPO
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details:

Provided as single-dose preservative-free vials containing 2,000, 3,000, 4,000 or 10,000 units of epoetin alfa per milliliter in citrate-buffered formulation.
The starting dose will be 25 IU/kg, administered s.c., t.i.w (i.e. a total dose of 75 IU/kg per week) and will be titrated individually in order to achieve stable Hb concentrations of 10.0-11.0 g/dl.

Arm title	Procrit
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	recombinant human epoetin alfa
Investigational medicinal product code	Procrit
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details:

Provided as single-dose preservative-free vials. Each 1 ml of solution contains 2,000, 3,000, 4,000 or 10,000 units of epoetin alfa.
The starting dose will be 25 IU/kg, administered s.c., t.i.w (i.e. a total dose of 75 IU/kg per week) and will be titrated individually in order to achieve stable Hb concentrations of 10.0-11.0 g/dl.

Number of subjects in period 2	APO-EPO	Procrit
Started	319	166
Completed	293	152
Not completed	26	14
Adverse event, serious fatal	4	3
Consent withdrawn by subject	7	6
Adverse event, non-fatal	5	3
Need for rescue medication	1	-
Administrative problems	1	-
Prohibited concomitant medication	1	-
Other not specified	7	2

Baseline characteristics

Reporting groups

Reporting group title	APO-EPO

Reporting group description:

APO-EPO as recombinant human epoetin alfa was developed as a proposed biosimilar to the US-registered epoetin alfa Procrit®. The product contains the identical amino acid sequence as an isolated natural EPO. It was administered s.c., t.i.w. and was titrated individually according to the pre-specified rules to achieve stable Hb concentrations

Reporting group title	Procrit

Reporting group description:

Procrit is a recombinant human epoetin alfa, has the same biological effects as endogenous EPO. It was administered s.c., t.i.w. and was titrated individually according to the pre-specified rules to achieve stable Hb concentrations

Reporting group values	APO-EPO	Procrit	Total
Number of subjects	355	178	533
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Age in years at screening			
Units: years			
arithmetic mean	54.74	53.85	
standard deviation	± 14.78	± 14.17	-
Gender categorical			
Units: Subjects			
Female	142	71	213
Male	213	107	320
Residual renal function			
Units: Subjects			
Urine output < 1000 ml/day	299	152	451
Urine output >= 1000ml/day	56	26	82

Subject analysis sets

Subject analysis set title	Intention-to-Treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT analysis set comprised of all randomized subjects who received at least one dose of study drug and who provided at least one post-baseline Hb measurement. The ITT analysis set was

analyzed as randomized, except for the primary endpoint, which was analyzed both “as randomized” and “as treated”.

Subject analysis set title	Modified Intention-to-Treat
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

As both co-primary endpoints were based on Evaluation Phase data only, the mITT analysis set included those subjects who started this phase and had available measurements for at least one of the 2 co-primary endpoints in the Evaluation Phase (measured between Week 21-24). The mITT analysis set was analyzed both “as randomized” and “as treated”.

Subject analysis set title	Per protocol
Subject analysis set type	Per protocol

Subject analysis set description:

The PP analysis set comprised of all subjects from the mITT analysis set who had no major PDs that affected the interpretation of the primary and co-primary endpoints had completed at least 2 weeks in the Evaluation Phase, and whose mean Hb level during the Evaluation Phase was maintained in the prescribed interval of 10-11 g/dL. Major PDs and their impact on primary and co-primary endpoints were defined in the Protocol Deviation Handling Plan and were assessed during the Blinded Data Review Meeting.

Reporting group values	Intention-to-Treat	Modified Intention-to-Treat	Per protocol
Number of subjects	530	489	223
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age in years at screening			
Units: years			
arithmetic mean	54.49	54.58	56.27
standard deviation	± 14.56	± 14.41	± 13.80
Gender categorical Units: Subjects			
Female	213	192	95
Male	317	297	128
Residual renal function Units: Subjects			
Urine output < 1000 ml/day	448	412	192
Urine output >= 1000ml/day	82	77	31

End points

End points reporting groups

Reporting group title	APO-EPO

Reporting group description:

APO-EPO as recombinant human epoetin alfa was developed as a proposed biosimilar to the US-registered epoetin alfa Procrit®. The product contains the identical amino acid sequence as an isolated natural EPO. It was administered s.c., t.i.w. and was titrated individually according to the pre-specified rules to achieve stable Hb concentrations

Reporting group title	Procrit

Reporting group description:

Procrit is a recombinant human epoetin alfa, has the same biological effects as endogenous EPO. It was administered s.c., t.i.w. and was titrated individually according to the pre-specified rules to achieve stable Hb concentrations

Reporting group title	APO-EPO

Reporting group description: -

Reporting group title	Procrit

Reporting group description: -

Subject analysis set title	Intention-to-Treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT analysis set comprised of all randomized subjects who received at least one dose of study drug and who provided at least one post-baseline Hb measurement. The ITT analysis set was analyzed as randomized, except for the primary endpoint, which was analyzed both “as randomized” and “as treated”.

Subject analysis set title	Modified Intention-to-Treat
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

As both co-primary endpoints were based on Evaluation Phase data only, the mITT analysis set included those subjects who started this phase and had available measurements for at least one of the 2 co-primary endpoints in the Evaluation Phase (measured between Week 21-24). The mITT analysis set was analyzed both “as randomized” and “as treated”.

Subject analysis set title	Per protocol
Subject analysis set type	Per protocol

Subject analysis set description:

The PP analysis set comprised of all subjects from the mITT analysis set who had no major PDs that affected the interpretation of the primary and co-primary endpoints had completed at least 2 weeks in the Evaluation Phase, and whose mean Hb level during the Evaluation Phase was maintained in the prescribed interval of 10-11 g/dL. Major PDs and their impact on primary and co-primary endpoints were defined in the Protocol Deviation Handling Plan and were assessed during the Blinded Data Review Meeting.

Primary: Mean dose of epoetin (mITT)

End point title	Mean dose of epoetin (mITT)

End point description:

Mean weekly dose of epoetin per kilogram of body weight necessary to maintain hemoglobin within 10.0-11.0 g/dL level during the last 4 weeks of the correction phase

End point type	Primary

End point timeframe:

Last 4 weeks of correction phase (Week 21-24)

End point values	APO-EPO	Procrit	Modified Intention-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	323	166	0[1]	
Units: IU/kg				
least squares mean (confidence interval 95%)	54.85 (50.20 to 59.49)	54.86 (48.51 to 61.21)	(to)	

Notes:

[1] - Analysis set was analysed by reporting group.

Statistical analyses

Statistical analysis title	Equivalence in mean weekly dose

Statistical analysis description:

95% CI for the mean treatment difference (APO-EPO - Procrit) was calculated within a mixed model framework accounting for treatment arm, week, and residual renal function at screening

Comparison groups	Procrit v APO-EPO
Number of subjects included in analysis	489
Analysis specification	Pre-specified
Analysis type	equivalence[2]
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.19
upper limit	7.16

Notes:

[2] - Treatment was considered as randomized.
Acceptance interval for equivalence was [-45 IU/kg, 45 IU/kg]

Primary: Mean hemoglobin concentration (mITT)

End point title	Mean hemoglobin concentration (mITT)

End point description:

Mean hemoglobin concentration during the last 4 weeks of the correction phase

End point type	Primary

End point timeframe:

Last 4 weeks of correction phase (Week 21-24)

End point values	APO-EPO	Procrit	Modified Intention-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	323	166	0[3]	
Units: g/dL				
least squares mean (confidence interval 95%)	10.54 (10.43 to 10.65)	10.48 (10.35 to 10.62)	(to)	

Notes:

[3] - Analysis set was analysed by reporting group.

Statistical analyses

Statistical analysis title	Equvalence in mean hemoglobin concentration

Statistical analysis description:

95% CI for the mean treatment difference (APO-EPO - Procrit) was calculated within a mixed model framework accounting for treatment arm, week, and residual renal function at screening

Comparison groups	APO-EPO v Procrit
Number of subjects included in analysis	489
Analysis specification	Pre-specified
Analysis type	equivalence[4]
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.21

Notes:

[4] - Treatment was considered as randomized.
Acceptance interval for equivalence was [-0.5 g/L, 0.5 g/L]

Secondary: Subjects with treatment success

End point title	Subjects with treatment success

End point description:

Number and proportion of subjects with treatment success, i.e. Hb concentration between 10.0 - 11.0 g/dL for 2 consecutive weeks without any blood transfusion within the preceding 3 months.

End point type	Secondary

End point timeframe:

Correction phase, at each two consecutive weeks (Week 23-24 is presented).

End point values	APO-EPO	Procrit	Intention-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	312	163	0[5]	
Units: Number of subjects	111	59		

Notes:

[5] - Analysis set was analysed by reporting group.

Statistical analyses

Statistical analysis title	Equivalence in treatment success

Statistical analysis description:

Percent difference between arms (APO-EPO – Procrit) and the Miettinen-Nurminen confidence limits for

differences between success rates were calculated.

Comparison groups	Procrit v APO-EPO
Number of subjects included in analysis	475
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Risk difference (RD)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.8
upper limit	8.3

Secondary: Subjects needing blood transfusions

End point title	Subjects needing blood transfusions

End point description:

Proportion of subjects needing blood transfusions during the treatment period.

End point type	Secondary

End point timeframe:

Treatment period

End point values	APO-EPO	Procrit	Intention-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	350	177	0[6]	
Units: number of subjects	5	4		

Notes:

[6] - Analysis set was analysed by reporting group.

Statistical analyses

Statistical analysis title	Equivalence in number of transfusions
Comparison groups	APO-EPO v Procrit
Number of subjects included in analysis	527
Analysis specification	Pre-specified
Analysis type	equivalence[7]
Parameter estimate	Risk difference (RD)
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	1.5

Notes:

[7] - Percent difference between arms (APO-EPO – Procrit) and the Miettinen-Nurminen confidence limits for differences between success rates were calculated.

Secondary: Subjects with maintenance success

End point title	Subjects with maintenance success

End point description:

Number and proportion of subjects with the maintenance success (maintenance of mean Hb concentration of 10.0-11.0 g/dL for at least 4 consecutive weeks in the Maintenance Phase) without any blood transfusion within the preceding 3 months.

End point type	Secondary

End point timeframe:

4 consecutive weeks in the Maintenance phase (Week 44-48 is presented)

End point values	APO-EPO	Procrit	Intention-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	291	152	0[8]	
Units: Number of patients	63	27		

Notes:

[8] - Analysis set was analysed by reporting group.

Statistical analyses

Statistical analysis title	Equivalence in maintenance success

Statistical analysis description:

Proportion of subjects with maintenance success.

Comparison groups	Procrit v APO-EPO
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	equivalence[9]
Parameter estimate	Risk difference (RD)
Point estimate	3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	11.3

Notes:

[9] - Percent difference between arms (APO-EPO – Procrit) and the Miettinen-Nurminen confidence limits for differences between success rates were calculated.

Secondary: Subjects with hemoglobin <10.0 g/dL

End point title	Subjects with hemoglobin <10.0 g/dL

End point description:

Number and proportion of subjects with Hb values outside the target range (<10.0 g/dL) (in the Correction and Maintenance Phases, by visit);

End point type	Secondary

End point timeframe:

In the correction and maintenance phase, by visit (week 24 and week 48 are presented)

End point values	APO-EPO	Procrit	APO-EPO	Procrit
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	319	166	296	152
Units: Number of subjects	81	44	71	43

End point values	Intention-to-Treat			
Subject group type	Subject analysis set			
Number of subjects analysed	485			
Units: Number of subjects	125			

Statistical analyses

Statistical analysis title	Equivalence in number of subjects with Hb <10g/dL

Statistical analysis description:

Proportion of subjects with hemoglobin result outside the target range (<10 g/dL) at the end of the correction phase (week 24).

Comparison groups	APO-EPO v Procrit
Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	equivalence[10]
Parameter estimate	Risk difference (RD)
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.6
upper limit	6.9

Notes:

[10] - Percent difference between arms (APO-EPO – Procrit) and the Miettinen-Nurminen confidence limits for differences between risk rates were calculated.

Statistical analysis title	Equivalence in number of subjects with Hb <10g/dL

Statistical analysis description:

Proportion of subjects with hemoglobin result outside the target range (<10 g/dL) at the end of the maintenance phase (week 48).

Comparison groups	APO-EPO v Procrit
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	equivalence[11]
Parameter estimate	Risk difference (RD)
Point estimate	-4.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.2
upper limit	4.1

Notes:

[11] - Percent difference between arms (APO-EPO – Procrit) and the Miettinen-Nurminen confidence limits for differences between risk rates were calculated.

Secondary: Subjects with hemoglobin >11.0 g/dL

End point title	Subjects with hemoglobin >11.0 g/dL

End point description:

Number and proportion of subjects with Hb values outside the target range (>11.0 g/dL) (in the Correction and Maintenance Phases, by visit);

End point type	Secondary

End point timeframe:

In the correction and maintenance phase, by visit (week 24 and week 48 are presented)

End point values	APO-EPO	Procrit	APO-EPO	Procrit
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	319	166	296	152
Units: subjects outside the target	76	33	111	55

End point values	Intention-to-Treat			
Subject group type	Subject analysis set			
Number of subjects analysed	0[12]			
Units: subjects outside the target				

Notes:

[12] - Analysis set was analysed by reporting group.

Statistical analyses

Statistical analysis title	Equivalence in number of subjects with Hb >11g/dL

Statistical analysis description:

Proportion of subjects with hemoglobin result outside the target range (>11 g/dL) at the end of the correction phase (week 24).

Comparison groups	APO-EPO v Procrit
Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	equivalence[13]
Parameter estimate	Risk difference (RD)
Point estimate	3.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1
upper limit	11.3

Notes:

[13] - Percent difference between arms (APO-EPO – Procrit) and the Miettinen-Nurminen confidence limits for differences between risk rates were calculated.

Statistical analysis title	Equivalence in number of subjects with Hb >11g/dL

Statistical analysis description:

Proportion of subjects with hemoglobin result outside the target range (>11 g/dL) at the end of the maintenance phase (week 48).

Comparison groups	APO-EPO v Procrit
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	equivalence[14]
Parameter estimate	Risk difference (RD)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.2
upper limit	10.5

Notes:

[14] - Percent difference between arms (APO-EPO – Procrit) and the Miettinen-Nurminen confidence limits for differences between risk rates were calculated.

Secondary: Subjects with hematocrit >30%

End point title	Subjects with hematocrit >30%

End point description:

Number and proportion of subjects with hematocrit measurements > 30%.

End point type	Secondary

End point timeframe:

In the correction and maintenance phase, by visit (week 24 and week 48 are presented)

End point values	APO-EPO	Procrit	APO-EPO	Procrit
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	319	166	296	152
Units: number of subjects	234	110	224	106

End point values	Intention-to-Treat			
Subject group type	Subject analysis set			
Number of subjects analysed	0[15]			
Units: number of subjects				

Notes:

[15] - Analysis set was analysed by reporting group.

Statistical analyses

Statistical analysis title	Equivalence in treatment success (hematocrit>30%)
Statistical analysis description:	
Proportion of subjects with hemotocrit >30% at the end of the correction phase (week 24).	
Comparison groups	APO-EPO v Procrit
Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	equivalence[16]
Parameter estimate	Risk difference (RD)
Point estimate	7.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	15.9

Notes:

[16] - Percent difference between arms (APO-EPO – Procrit) and the Miettinen-Nurminen confidence limits for differences between success rates were calculated.

Statistical analysis title	Equivalence in treatment success (hematocrit>30%)
Statistical analysis description:	
Proportion of subjects with hemotocrit >30% at the end of the maintenance phase (week 48).	
Comparison groups	APO-EPO v Procrit
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	equivalence[17]
Parameter estimate	Risk difference (RD)
Point estimate	5.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	14.9

Notes:

[17] - Percent difference between arms (APO-EPO – Procrit) and the Miettinen-Nurminen confidence limits for differences between success rates were calculated.

Secondary: Subjects with i.v. iron supplementation

End point title	Subjects with i.v. iron supplementation
End point description:	
Number and proportion of subjects with TSAT < 20% or ferritin < 100 ng/mL and requiring i.v. supplementation of iron.	
End point type	Secondary
End point timeframe:	
In the correction and maintenance phase, by visit (week 24 and week 48 are presented)	

End point values	APO-EPO	Procrit	APO-EPO	Procrit
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	318	166	295	149
Units: number of subjects	28	19	14	13

End point values	Intention-to-Treat			
Subject group type	Subject analysis set			
Number of subjects analysed	0[18]			
Units: number of subjects				

Notes:

[18] - Analysis set was analysed by reporting group.

Statistical analyses

Statistical analysis title	Equivalence in iron supplementation

Statistical analysis description:

Proportion of subjects at the end of the correction phase (week 24).

Comparison groups	APO-EPO v Procrit
Number of subjects included in analysis	484
Analysis specification	Pre-specified
Analysis type	equivalence[19]
Parameter estimate	Risk difference (RD)
Point estimate	-2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9
upper limit	2.8

Notes:

[19] - Percent difference between arms (APO-EPO – Procrit) and the Miettinen-Nurminen confidence limits for differences between risk rates were calculated.

Statistical analysis title	Equivalence in iron supplementation

Statistical analysis description:

Proportion of subjects with hemoglobin result outside the target range (<10 g/dL) at the end of the maintenance phase (week 48).

Comparison groups	APO-EPO v Procrit
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	equivalence[20]
Parameter estimate	Risk difference (RD)
Point estimate	-4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-10
upper limit	0.7

Notes:

[20] - Percent difference between arms (APO-EPO – Procrit) and the Miettinen-Nurminen confidence limits for differences between risk rates were calculated.

Other pre-specified: Mean dose of epoetin (PP)

End point title	Mean dose of epoetin (PP)

End point description:

Supportive analysis of the co-primary endpoint in the per protocol analysis set.
Mean weekly dose of epoetin per kilogram of body weight necessary to maintain hemoglobin within 10.0-11.0 g/dL level during the last 4 weeks of the correction phase.

End point type	Other pre-specified

End point timeframe:

Last 4 weeks of correction phase (Week 21-24)

End point values	APO-EPO	Procrit	Per protocol	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	141	82	0[21]	
Units: IU/kg				
least squares mean (confidence interval 95%)	56.16 (50.02 to 62.31)	7.89 (-1.23 to 17.00)	(to)	

Notes:

[21] - Analysis set was analysed by reporting group.

Statistical analyses

Statistical analysis title	Equivalence in mean weekly dose (supporting)

Statistical analysis description:

95% CI for the mean treatment difference (APO-EPO - Procrit) was calculated within a mixed model framework accounting for treatment arm, week, and residual renal function at screening

Comparison groups	APO-EPO v Procrit
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	equivalence[22]
Parameter estimate	Mean difference (final values)
Point estimate	7.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.23
upper limit	17

Notes:

[22] - Treatment was considered as randomized.
Acceptance interval for equivalence was [-45 IU/kg, 45 IU/kg]

Other pre-specified: Mean hemoglobin concentration (PP)

End point title	Mean hemoglobin concentration (PP)

End point description:

End point type	Other pre-specified

End point timeframe:

Last 4 weeks of correction phase (Week 21-24)

End point values	APO-EPO	Procrit	Per protocol	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	141	82	0[23]	
Units: g/dL				
least squares mean (confidence interval 95%)	10.50 (10.45 to 10.56)	10.53 (10.46 to 10.60)	(to)	

Notes:

[23] - Analysis set was analysed by reporting group.

Statistical analyses

Statistical analysis title	Equvalence in mean hemoglobin (supporting)

Statistical analysis description:

95% CI for the mean treatment difference (APO-EPO - Procrit) was calculated within a mixed model framework accounting for treatment arm, week, and residual renal function at screening.

Comparison groups	APO-EPO v Procrit
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	equivalence[24]
Parameter estimate	Mean difference (final values)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.05

Notes:

[24] - Supporting analysis for the co-primary endpoint on the per protocol analysis set.
Treatment was considered as randomized.
Acceptance interval for equivalence was [-0.5 g/dL, 0.5 g/dL].

Other pre-specified: Mean dose of epoetin (imputed ITT)

End point title	Mean dose of epoetin (imputed ITT)

End point description:

Mean weekly dose of epoetin per kilogram of body weight necessary to maintain hemoglobin within 10.0-11.0 g/dL level during the last 4 weeks of the correction phase.
Multiple imputation was performed for all subjects with missing data in the ITT analysis set.

End point type	Other pre-specified

End point timeframe:

Last 4 weeks of correction phase (Week 21-24)

End point values	APO-EPO	Procrit	Intention-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	352	178	0[25]	
Units: IU/kg				
least squares mean (confidence interval 95%)	53.15 (48.69 to 57.61)	51.51 (45.38 to 57.64)	(to)	

Notes:

[25] - Analysis set was analysed by reporting group.

Statistical analyses

Statistical analysis title	Equivalence in mean weekly dose (supporting)

Statistical analysis description:

Supporting analysis for the co-primary endpoint on the ITT analysis set after multiple imputation.

Comparison groups	APO-EPO v Procrit
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	equivalence[26]
Parameter estimate	Mean difference (final values)
Point estimate	1.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.34
upper limit	8.62

Notes:

[26] - Treatment was considered as randomized.
Acceptance interval for equivalence was [-45 IU/kg, 45 IU/kg].

Other pre-specified: Mean hemoglobin concentration (imputed ITT)

End point title	Mean hemoglobin concentration (imputed ITT)

End point description:

95% CI for the mean treatment difference (APO-EPO - Procrit) was calculated within a mixed model framework accounting for treatment arm, week, and residual renal function at screening.
Multiple imputation was performed for all subjects with missing data in the ITT analysis set.

End point type	Other pre-specified

End point timeframe:

Last 4 weeks of correction phase (Week 21-24)

End point values	APO-EPO	Procrit	Intention-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	352	178	0[27]	
Units: g/dL				
least squares mean (confidence interval 95%)	10.48 (10.36 to 10.59)	10.45 (10.31 to 10.59)	(to)	

Notes:

[27] - Analysis set was analysed by reporting group.

Statistical analyses

Statistical analysis title	Equvalence in mean hemoglobin (supporting)

Statistical analysis description:

Supporting analysis for the co-primary endpoint on the ITT analysis set after multiple imputation.

Comparison groups	APO-EPO v Procrit
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	equivalence[28]
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.19

Notes:

[28] - Treatment was considered as randomized.
Acceptance interval for equivalence was [-0.5 g/dL, 0.5 g/dL].

Other pre-specified: Mean dose of epoetin (mITT as treated)

End point title	Mean dose of epoetin (mITT as treated)

End point description:

95% CI for the mean treatment difference (APO-EPO - Procrit) was calculated within a mixed model framework accounting for treatment arm, week, and residual renal function at screening.

End point type	Other pre-specified

End point timeframe:

Last 4 weeks of correction phase (Week 21-24)

End point values	APO-EPO	Procrit	Modified Intention-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	322	167	0[29]	
Units: IU/kg				
least squares mean (confidence interval 95%)	54.83 (50.18 to 59.48)	54.89 (48.57 to 61.21)	(to)	

Notes:

[29] - Analysis set was analysed by reporting group.

Statistical analyses

Statistical analysis title	Equivalence in mean weekly dose (sensitivity)
Statistical analysis description:	
Sensitivity analysis.	
Comparison groups	APO-EPO v Procrit
Number of subjects included in analysis	489
Analysis specification	Pre-specified
Analysis type	equivalence[30]
Parameter estimate	Mean difference (final values)
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.21
upper limit	7.1

Notes:

[30] - Treatment was considered as treated.
Acceptance interval for equivalence was [-45 IU/kg, 45 IU/kg].

Other pre-specified: Mean hemoglobin concentration (mITT as treated)

End point title	Mean hemoglobin concentration (mITT as treated)
End point description:	
95% CI for the mean treatment difference (APO-EPO - Procrit) was calculated within a mixed model framework accounting for treatment arm, week, and residual renal function at screening.	
End point type	Other pre-specified
End point timeframe:	
Last 4 weeks of correction phase (Week 21-24)	

End point values	APO-EPO	Procrit	Modified Intention-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	322	167	489	
Units: g/dL				
least squares mean (confidence interval 95%)	10.54 (10.43 to 10.64)	10.49 (10.35 to 10.62)	0.05 (-0.11 to 0.20)	

Statistical analyses

Statistical analysis title	Equvalence in mean hemoglobin (sensitivity)
Statistical analysis description:	
Sensitivity analysis.	
Comparison groups	Procrit v APO-EPO

Number of subjects included in analysis	489
Analysis specification	Pre-specified
Analysis type	equivalence[31]
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.2

Notes:

[31] - Treatment was considered as treated.
Acceptance interval for equivalence was [-0.5 g/dL, 0.5 g/dL].

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first study drug administration until the last study visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	APO-EPO

Reporting group description:

Considering a frequency threshold of 5% for non-serious adverse events.

Reporting group title	Procrit

Reporting group description:

Considering the frequency threshold of 5% for non-serious adverse events.

Serious adverse events	APO-EPO	Procrit	
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 351 (10.83%)	20 / 179 (11.17%)	
number of deaths (all causes)	10	3	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	0 / 351 (0.00%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	2 / 351 (0.57%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			

subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Vascular disorders			
Extremity necrosis			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral artery embolism			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 351 (0.00%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 351 (0.57%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hypertensive emergency			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic venous thrombosis			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			

subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Nephrectomy			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Removal of renal transplant			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal transplant			
subjects affected / exposed	2 / 351 (0.57%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 351 (0.00%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Medical device complication			
subjects affected / exposed	0 / 351 (0.00%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 351 (0.00%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Thrombosis in device			
subjects affected / exposed	0 / 351 (0.00%)	2 / 179 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic ovarian cyst			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute respiratory failure			
subjects affected / exposed	2 / 351 (0.57%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 351 (0.00%)	2 / 179 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
Arteriovenous fistula aneurysm			

subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula thrombosis			
subjects affected / exposed	2 / 351 (0.57%)	3 / 179 (1.68%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	2 / 351 (0.57%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Shunt malfunction			
subjects affected / exposed	1 / 351 (0.28%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access complication			
subjects affected / exposed	0 / 351 (0.00%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft thrombosis			

subjects affected / exposed	0 / 351 (0.00%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Cerebrovascular accident			
subjects affected / exposed	3 / 351 (0.85%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
Coma			
subjects affected / exposed	2 / 351 (0.57%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Convulsion			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	0 / 351 (0.00%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Grand mal convulsion			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic disorder			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Duodenal ulcer			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 351 (0.00%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 351 (0.00%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	3 / 351 (0.85%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 351 (0.00%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Cholecystitis			
subjects affected / exposed	1 / 351 (0.28%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	0 / 351 (0.00%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermal cyst			
subjects affected / exposed	0 / 351 (0.00%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acute endocarditis			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Appendicitis perforated			
subjects affected / exposed	0 / 351 (0.00%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 351 (0.00%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter sepsis			

subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	0 / 351 (0.00%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected dermal cyst			
subjects affected / exposed	0 / 351 (0.00%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 351 (0.00%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 351 (1.42%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Pneumonia bacterial			

subjects affected / exposed	0 / 351 (0.00%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis chronic			
subjects affected / exposed	1 / 351 (0.28%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyonephrosis			
subjects affected / exposed	0 / 351 (0.00%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 351 (0.28%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	APO-EPO	Procrit	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 351 (12.82%)	26 / 179 (14.53%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	24 / 351 (6.84%)	11 / 179 (6.15%)	
occurrences (all)	42	12	
Nervous system disorders			
Headache			
subjects affected / exposed	24 / 351 (6.84%)	15 / 179 (8.38%)	
occurrences (all)	31	21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 June 2012	Global Amendment 1
29 October 2012	Global Amendment 2
22 April 2013	Global Amendment 3
25 June 2013	Global Amendment 4
28 February 2014	Global Amendment 5
07 April 2015	Global Amendment 6
09 July 2015	Global Amendment 7

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported