2. Synopsis of Final Study Report

NAME OF COMPANY **STADA R&D GmbH** **NAME OF FINISHED PRODUCT:** **Epoetin STADA** **NAME OF ACTIVE INGREDIENT(S):** **epoetin**	**INDIVIDUAL STUDY TABLE REFERRING TO CLINICAL DOCUMENTATION OF THE DOSSIER:** **Volume:** **Page:**	*(FOR NATIONAL AUTHORITY USE ONLY)*

Title of the study:

Evaluation of the Therapeutic Equivalence of Two Different Formulations Containing Epoetin (Epoetin STADA vs. Erypo®) Administered Subcutaneously for the Maintenance Treatment of Renal Anaemia

Investigator(s):

Coordinating investigator:

Principal investigators:

Centre 01_BG:
Centre 02_BG:
Centre 03_BG:
Centre 04_BG:
Centre 05_BG:
Centre 06_BG:
Centre 07_BG:
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Centre 10_BG:
Centre 11_BG:
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Centre 13_BG:
Centre 14_BG:
Centre 15_BG:
Centre 16_BG:
Centre 17_BG:

Centre 01_DE:

Centre 01_PL:
Centre 02_PL:
Centre 03_PL:
Centre 04_PL:
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Centre 15_PL:
Centre 16_PL:
Centre 17_PL:
Centre 18_PL:
Centre 19_PL:
Centre 20_PL:
Centre 21_PL:
Centre 22_PL:

Centre 01_RO:
Centre 02_RO:
Centre 03_RO:
Centre 04_RO:
Centre 05_RO:

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Principal investigators:
Centre 01_RS:
Centre 02_RS:
Centre 03_RS:
Centre 04_RS:

BG: Bulgaria; DE: Germany; PL: Poland; RO: Romania; RS: Serbia

Study centres - main study phase:

n=42

14 centres in Bulgaria, 1 centre in Germany, 18 centres in Poland, 5 centres in Romania, 4 centres in Serbia

Study centres - open follow-up extension period (up to 54 weeks):

n=35

14 centres in Bulgaria, 15 centres in Poland, 3 centres in Romania, 3 centres in Serbia

Publication (reference):

Results of main study phase

Krivoshiev S, Wizemann V, Czekalski S, et al.: Therapeutic equivalence of epoetin zeta and alfa, administered subcutaneously, for maintenance treatment of renal anemia. Adv Ther. 2010 Feb;27(2):105-117. Epub 2010 Mar 30.

Studied period:		**Phase of development:**
date of first enrolment:	06-Feb-2008	Phase III
date of last completion main study:	01-Apr-2009	
date of last completion whole trial:	19-Apr-2010	

Objectives:

The primary objective of the present trial was to prove the therapeutic equivalence of Epoetin STADA to a reference product (Erypo®) administered subcutaneously for maintaining the haemoglobin concentration in anaemic patients with end-stage renal failure on chronic haemodialysis.

The secondary objective of the present trial was to gather data regarding the safety and tolerability of Epoetin STADA (with particular focus on the formation of anti-epoetin antibodies) when administered subcutaneously.

The aim of the open follow-up extension period was to gather data regarding the long-term safety, tolerability, and efficacy of Epoetin STADA under open, non-controlled conditions.

Study design - main study:	**Study design - open follow-up extension period:**
• Randomised • Observer-blind • Verum-controlled • Multiple-dose • Multicentre • Parallel groups of patients • Phase III • International • 500 patients planned for randomisation • Subcutaneous administration (1-3 times weekly at the end of dialysis)	• Open • Non-controlled • Multiple-dose • Multicentre • Phase III • International • Subcutaneous administration (1-3 times weekly at the end of dialysis)

Subjects (planned and analyzed):		
	planned for completion:	400
	screened:	707
	enrolled:	679
	randomised:	462
	drop-outs after randomisation:	78
	evaluated:	
	– safety population (run-in phase):	679
	– safety population (main phase):	462 (232 Test, 230 Reference)
	– full analysis set:	450 (228 Test, 222 Reference)
	– per protocol set:	319 (154 Test, 165 Reference)
	entered open follow-up extension period:	346
	evaluated:	346

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Diagnosis and criteria for selection:

Inclusion criteria:

- male or female patients, aged 18-75 years
- haemodialysis patients with end-stage renal failure and renal anaemia currently on epoetin treatment for at least 3 months
- patients on stable, adequate dialysis for at least three months (defined as no clinically relevant changes of dialysis regimen and/or dialyser)
- informed consent given in a written form after being provided with detailed information about the nature, risks, and scope of the clinical trial as well as the expected desirable and adverse effects of the drug.

Exclusion:

- contraindication for the test drug
- relative or absolute iron deficiency at the end of run-in period
- myelodysplastic syndrome
- documented bleeding disorders
- platelet count below $100x10^9$/l
- known, clinically manifested deficiency of folic acid and/or vitamin B12 (irrespective whether currently treated or not)
- known bone marrow fibrosis (osteitis fibrosa cystica)
- clinically relevant changes of dialysis regimen and/or dialyser during the trial
- clinically relevant increase of CRP (higher than 10 mg/dl) for at least 2 weeks
- any blood transfusion within the last 3 months prior main study phase
- acute bleeding and/or recently documented haemorrhage
- hypersensitivity to epoetin
- epoetin dosage > 3x200 IU/kg/week
- detectable anti-epoetin antibodies
- uncontrolled hypertension
- any of the following within the 6 months prior main study phase:
  - myocardial infarction,
  - stroke / cerebrovascular insult (minor stroke) or TIA (transient ischemic attack) / intracerebral bleeding / cerebral infarction,
  - severe/unstable angina,
  - coronary/peripheral artery bypass graft,
  - decompensated congestive heart failure (NYHA class III – IV),
  - cerebrovascular incident or transient ischemic attack,
  - pulmonary embolism,
  - deep vein thrombosis, or other thromboembolic event.
- known epilepsy
- liver cirrhosis with clinical evidence of complications (portal hypertension, splenomegaly, ascites)
- patients with confirmed aluminium intoxication
- confirmed, clinically relevant haemolysis and/or occult blood loss
- presence of malignant tumours
- clinically relevant malnutrition
- pregnancy or lactation period in female patients
- severe physical or mental concomitant diseases that might hamper the realisation of the trial according to protocol or the evaluation of efficacy or safety
- anamnestic or current alcohol abuse i.e. consumption of more than 10 units of alcohol per week or a history of alcoholism or drug/chemical abuse (one unit of alcohol equals 250 ml of beer, 125 ml wine or 25 ml of spirits)
- participation in another clinical trial with a different test drug than the one tested in the present trial within the last 12 weeks
- legal incapacity and/or other circumstances rendering the patient unable to understand the nature, scope and possible consequences of the study
- unreliability or lack of cooperation
- lack of a possibility to attend the visits required by protocol.

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Test product, dose and mode of administration, batch number:	name: manufacturer: unit dose: mode/route: regimen: **1000 IU epoetin** batch nos. and expiry dates: **2000 IU epoetin** batch nos. and expiry dates: **3000 IU epoetin** batch nos. and expiry dates: **4000 IU epoetin** batch nos. and expiry dates: **5000 IU epoetin** batch nos. and expiry dates:	Epoetin STADA STADA Arzneimittel AG, Germany 1000, 2000, 3000, 4000, or 5000 IU epoetin subcutaneous / 1 pre-filled syringe 1-3 times weekly	

* Batches 337 and 338 were delivered, but not used.

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Reference product, dose and mode of administration, batch number:	name:	Erypo®
	manufacturer:	JANSSEN-CILAG GmbH, Germany
	unit dose:	1000, 2000, 3000, 4000, or 5000 IU epoetin
	mode/route:	subcutaneous / 1 pre-filled syringe
	regimen:	1-3 times weekly
	1000 IU epoetin batch nos. and expiry dates:	
	2000 IU epoetin batch nos. and expiry dates:	
	3000 IU epoetin batch nos. and expiry dates:	
	4000 IU epoetin batch nos. and expiry dates:	
	5000 IU epoetin batch nos. and expiry dates:	

Duration of treatment:

Observer-blind main study phase of 28 weeks with either the test product (Epoetin STADA) or the reference product (Erypo®), preceded by an open run-in period of 12-16 weeks with Epoetin STADA. After the end of the 28 weeks main study phase, all patients could continue treatment for further 54 weeks with the test product as part of an open, follow-up extension period of the trial.

Criteria for evaluation:

Efficacy:

Primary endpoints:

- mean haemoglobin level during the last 4 weeks of treatment,
- mean weekly epoetin dosage per kg body weight during the last 4 weeks of treatment.

Secondary endpoints:

- mean haematocrit levels during main study phase,
- proportion of patients with any permanent changes of haemoglobin levels of more than 1 g/dl during main study phase,
- proportion of patients with any transient changes of haemoglobin levels of more than 1 g/dl during main study phase,
- proportion of patients with any permanent dose change during main study phase,
- proportion of patients with any transient dose change during main study phase,
- proportion of patients with any haemoglobin measurement outside the target range during main study phase,
- incidence of blood transfusions.

Safety:

Safety endpoints:

- incidence of haemoglobin levels above 13 g/dl,
- occurrence of anti-epoetin antibodies,
- ratings of tolerability,
- evaluation of adverse events.

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Statistical methods - main study:

From the statistical point of view, the question of therapeutic equivalence was approached by calculating the 95% confidence interval of the difference between both treatment groups of the primary endpoints:

- mean haemoglobin level during the last 4 weeks of treatment,
- mean weekly epoetin dosage per kg body weight during the last 4 weeks of treatment.

These confidence intervals were compared with the pre-defined clinical acceptance ranges for the corresponding parameters (± 0.5 g/dl for haemoglobin and ± 45 IU/kg/week for epoetin dosage, based on the respective reference means). The intervals were calculated by means of ANOVA.

The rationale for the choice of the relevant acceptance ranges regarding both primary endpoints are the ranges accepted by EMA regarding a previous trial of maintenance type with the same test product that was approved by the European Commission for placing on the market in the European Union on 18-Dec-2007.

The statistical evaluation of the primary endpoint “mean weekly epoetin dosage per kg body weight during the last 4 weeks of treatment” was performed based on the nominal dosage declared on the labels of the pre-filled syringes.

As the dosage of epoetin and the corresponding level of haemoglobin are closely interrelated, a hierarchic test strategy was used in the present trial. The test on a higher level of hierarchy can only be performed, should the target of the previous level be fulfilled. The overall equivalence statement is consistent with a positive outcome on both levels of hierarchy. Due to this reason, no adjustment of alpha values was required on the separate levels. The levels of hierarchy were defined as follows:

Level 1: Calculation of the 95% confidence interval of the difference (test - reference) of the mean haemoglobin level during the last 4 weeks of treatment and comparison with the pre-defined acceptance range.

Level 2: Calculation of the 95% confidence interval of the difference (test - reference) of the mean weekly epoetin dosage per kg body weight during the last 4 weeks of treatment and comparison with the pre-defined acceptance range.

The evaluation of the secondary and safety endpoints was performed according to the type of distribution of the respective parameter. A Chi-square test was applied for parameters with discrete distribution, a t-test or a Wilcoxon-Mann-Whitney test was applied for continuously distributed parameters.

The statistical analysis was performed on three different patient populations:

- Safety population (all patients who started therapy with randomised study medication).
- Full analysis set (all patients who were treated more than 4 weeks with randomised study medication).
- Per protocol population (excluding cases of major protocol violation and drop-outs).

Statistical methods - open follow-up extension period:

The statistical analysis of the results of the open follow-up extension period were only descriptive. Depending on their distribution the target parameters were presented with their means, SD, SEM, median and quartiles or with their incidences.

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RESULTS

Disposition of patients:

A total number of 707 male and female patients with end-stage renal failure on chronic haemodialysis were informed about the aim of the study and were screened after giving their consent in written form. After careful consideration of all inclusion and exclusion criteria, 28 patients were not eligible for the trial. Therefore, only 679 patients entered the open run-in treatment period with the test product (Epoetin STADA). After 12 to 18 weeks treatment 462 patients were eligible to start observer-blind treatment and were randomised to one of both study drugs (Epoetin STADA or Erypo®) (safety population). Two hundred and thirty-two patients were allocated to the test medication and 230 patients to the reference drug. Twelve patients (4 treated with test drug and 8 treated with the reference preparation) were excluded from the full analysis set (n=450). Further 131 patients were excluded from the per protocol set due to major protocol deviations. Therefore, the per protocol set consists of 319 patients.

A total number of 346 male and female patients who have completed the blinded treatment period of the trial (main study) started treatment with the test product Epoetin STADA in the open follow-up extension period.

Efficacy:

In the following all values of the weekly epoetin dosage of both study drugs refer to the nominal / labelled dosage. Additionally, a statistical evaluation taking into account the real bioactivity of the batches used was performed (see chapter 11).

Primary endpoints

The mean haemoglobin level during the last 4 weeks was 10.94 ± 0.84 g/dl for patients treated with Epoetin STADA and 11.02 ± 0.94 g/dl for patients treated with Erypo®. The 95% confidence interval of the difference (test - reference) of the mean haemoglobin level during the last 4 weeks of treatment (level 1 of the hierarchic test strategy) was between -0.28 g/dl and 0.12 g/dl and thus entirely within the pre-defined equivalence range (±0.5 g/dl).

The mean weekly epoetin dosage per kg body weight during the last 4 weeks of treatment was 97.0 ± 94.3 IU/kg/week (Epoetin STADA) and 86.0 ± 78.0 IU/kg/week (Erypo®). The 95% confidence interval of the difference (test - reference) of the mean weekly epoetin dosage per kg body weight during the last 4 weeks of treatment (level 2 of the hierarchic test strategy) was between -8.03 IU/kg/week and 30.00 IU/kg/week and thus also within the pre-defined equivalence range of ±45 IU/kg/week.

The 95% confidence intervals are within the pre-defined acceptance ranges for both primary endpoints. According to the criteria set in the study protocol it can be concluded that the test product Epoetin STADA is equivalent with the reference product Erypo® in respect of its clinical efficacy.

The results obtained for the full analysis set of patients are practically identical with those observed in the per protocol population.

The results of both primary endpoints (haemoglobin and dosage) are presented in tables TT 1 and TT 2 as well as in figures TF 1 and TF 2.

The graphical presentation demonstrates that both products, Epoetin STADA and Erypo®, are effective regarding their ability to maintain haemoglobin levels within the target range of 10.0-12.0 g/dl (10.5-11.5 ± 0.5 g/dl).

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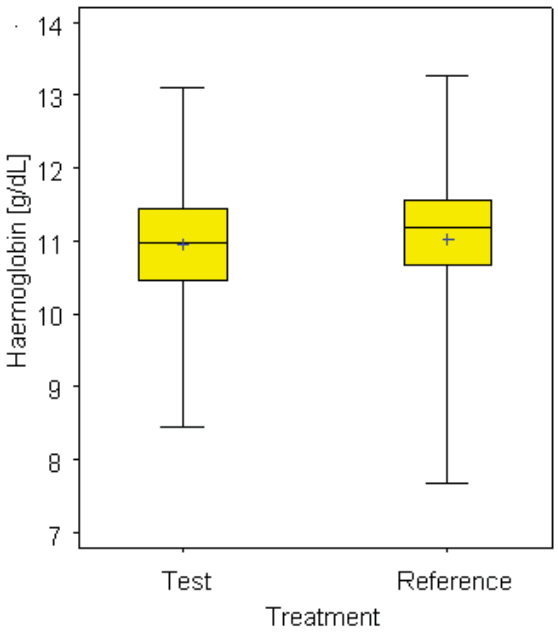
TT 1 Mean haemoglobin value [g/dl] over last 4 weeks - Descriptive statistics by treatment group, per protocol population

Treatment	Haemoglobin [g/dl]								
	ND	N	Mean	SD	Min	Q25	Median	Q75	Max
Test	0	154	10.94	0.84	8.45	10.45	10.98	11.45	13.10
Reference	0	165	11.02	0.94	7.68	10.68	11.18	11.55	13.28

TT 2 Mean epoetin dose [IU/week/kg BW] over last 4 weeks - Descriptive statistics by treatment group, per protocol population

Treatment	Epoetin dose [IU/kg/week]								
	ND	N	Mean	SD	Min	Q25	Median	Q75	Max
Test	0	154	97.0	94.3	12.4	39.6	65.4	107.2	555.6
Reference	0	165	86.0	78.0	8.5	36.0	62.5	115.4	482.5



TF 1 Mean haemoglobin level during the last 4 weeks of treatment

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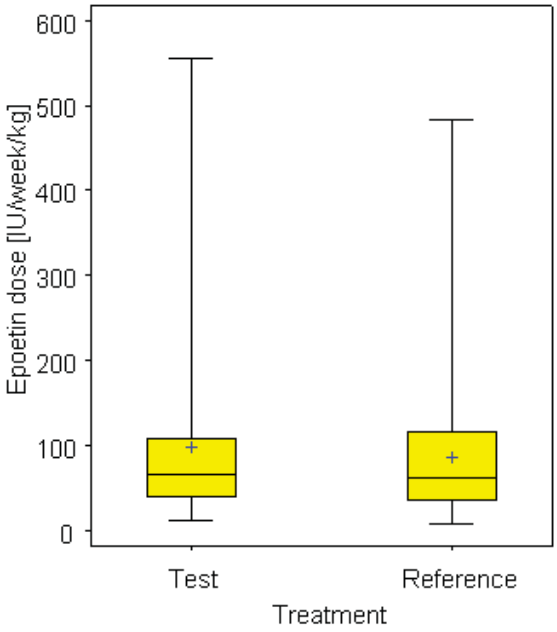

TF 2 Mean weekly epoetin dosage per kg body weight during the last 4 weeks of treatment

Secondary endpoints

All secondary endpoints confirmed the results obtained for the primary endpoints.

Mean haematocrit levels during main study phase:

The difference between the mean haematocrit levels during the main study phase for patients treated with Epoetin STADA and patients treated with Erypo® is minor and not statistically significant: 33.7 ± 2.0% (test) and 34.0 ± 1.9% (reference).

Proportion of patients with any permanent or transient changes of haemoglobin levels of more than 1 g/dl during main study phase:

In the group of patients treated with the test product 66 patients (42.9%) had a permanent and 131 patients (85.1%) had a transient change of haemoglobin of more than 1 g/dl. In the reference product group 59 patients (35.8%) had a permanent haemoglobin change, whilst 148 patients (89.7%) had a transient change.

Proportion of patients with any permanent or transient dose change during main study phase:

One hundred thirty-five patients (87.7%) treated with Epoetin STADA had a permanent and 139 patients (90.3%) had a transient dose change. A permanent dosage change in patients treated with Erypo® was necessary in 136 patients (82.4%), whilst transient dosage changes occurred in 141 patients (85.5%).

Proportion of patients with any haemoglobin measurement outside the target range during main study phase:

In the course of the treatment haemoglobin values outside the target range (10.0-12.0 g/dl) were observed in 134 patients (87.0%) of the Epoetin STADA group and in 143 patients (86.7%) of the Erypo® group.

Incidence of blood transfusions:

During the open run-in phase with the test product no blood transfusions were registered. In the course of the main study phase 2 single blood transfusions were performed in the test group (Epoetin STADA).

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Evaluation of efficacy parameters for the open follow-up extension period:

The mean nominal weekly epoetin dosage in the course of the open follow-up extension period was between 90.7 ± 84.5 IU/kg/week and 109.1 ± 98.2 IU/kg/week. The mean haemoglobin values, measured in monthly intervals, varied between 10.7 and 11.2 g/dl, and confirmed the observation of the main study that Epoetin STADA is effective to maintain haemoglobin levels between the target range of 10.0-12.0 g/dl (10.5-11.5 ± 0.5 g/dl). The mean haematocrit levels were between 32.6 and 34.4%. The incidences of transient/permanent Hb and dosage changes as well as the proportion of patients with any Hb value outside target range are similar to those observed in the main study. In the course of the follow-up period 16 patients received one blood transfusion; five patients needed 2 transfusions, and in one case 3 blood transfusions were necessary.

Safety:

Deaths

A total number of 11 patients died in the course of the open run-in phase with the test product (Epoetin STADA) before being randomised. The relationship between study medication and the serious adverse events, which led to the deaths, were assessed as not related in all cases.

During the observer-blind main study phase a total number of 23 patients died, 16 patients under treatment with the test drug and 7 patients under treatment with the reference product. These patients experienced 45 serious adverse events, which belonged mainly to the group of *nervous system disorders*, followed by *cardiac disorders* and *general disorders and administration site conditions*. Only in 1 case, a Serbian patient (#30138, random no. 377) who was treated with reference the relationship between study medication and the serious adverse events which led to death was assessed as possible. Additional to that in one case, a Bulgarian patient (#11113, random no. 156) who was treated with the test product the relationship between study medication and the serious adverse events which led to death was assessed as possible related by the sponsor, whilst investigator assessment was unlikely.

Additional analyses of deaths were performed in order to find out if there are any reasons for the imbalance in the number of deaths between test and reference group. Following parameters were evaluated: reasons for renal failure, previous diseases / medications, concomitant diseases / medications, haemoglobin levels, epoetin dose, blood pressure, withdrawals of study medication due to AE or SAE, deaths per centre and country, as well as the effect of additional risk factors by means of a logistic regression. The important results of these additional analyses are: Patients who died during treatment with the test preparation

- were clearly more severely ill as compared to the remaining patients in this group as they had a significantly higher incidence of myocardial ischaemia, diabetic neuropathy, chronic obstructive pulmonary disease, and aortic aneurysm;
- had lower haemoglobin levels as the remaining patients in this group;
- had significant higher epoetin doses as the remaining patients in this group.

The higher proportion of patients who died in Bulgaria was clearly related to the worse quality of dialysis in this country as shown by a significantly worse KT/V index as compared to all other countries. Further risk factors had no relevant effect on the incidence of cases of death.

A total number of 35 patients died in the course of the open follow-up extension period up to 54 weeks. The largest number of deaths is attributed or associated with cardiac disorders, infections and infestations, and nervous system disorders. In two cases (#11147 Cardiopulmonary failure, #30126 General disorders) the relationship between study medication and the serious adverse events which led to death were assessed as not assessable and in one case (#30111 Cerebrovascular accident) as possibly related. In all other cases no causal relationship between the intake of study drug and the serious adverse events which led to death were assessed and the serious adverse events which led to death was reported.

Adverse events and serious adverse events

The majority of serious adverse events (n=146) in the blind treatment period belonged to the SOC group of *surgical and medical procedures* (14.9% and 21.2% of all SAEs under test and reference treatment, respectively; mainly renal transplantation), *cardiac disorders* (13.8% and 17.3% of all SAEs under test and reference treatment, respectively; mainly arterial fibrillation), and *nervous system disorders* (14.9% and 13.5% of all SAEs under test and reference treatment, respectively; mainly haemorrhagic stroke).

Differences in frequency of adverse events in general and according to MedDRA SOCs between both treatment groups

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could not be observed.

The analysis of adverse events and serious adverse events, which included severity, outcome, relationship to study medication as well as the action taken with study medication revealed no differences between treatments.

The majority of serious adverse events (n=204) during the open follow-up extension period belonged to the group of *gastrointestinal disorders* (33 SAEs in 13 patients), followed by the groups of *infections and infestations* (31 SAEs in 24 patients), *cardiac disorders* (28 SAEs in 21 patients), and *surgical and medical procedures* (21 SAEs in 16 patients).

Incidence of haemoglobin levels above 13 g/dl

The incidence of haemoglobin levels above 13 g/dl was one of the safety endpoints in the present trial, because high haemoglobin values are associated with an increased risk of serious cardiovascular complications in patients with chronic renal failure. In more than 90% of patients no Hb values above 13 g/dl were registered in open run-in treatment period with the test product. In the main study phase the proportion of patients with no Hb values above 13 g/dl decreased (76.7% for the Epoetin STADA treatment group and 76.2% for the Erypo® treatment group) with no significant differences between both treatment groups.

In the course of the open follow-up extension period 83.2% of all patients had no Hb values above 13 g/dl.

Anti-epoetin antibodies

All patients were tested for the presence of anti-epoetin antibodies (last available blood sample). No case of anti-epoetin antibodies was noted in the very sensitive screening assay. Furthermore, no clinical signs for pure red cell aplasia were observed in any patient in the course of the whole trial (main study and open follow-up extension period).

Ratings of tolerability

Both products showed a very good overall and local tolerability without any evidence of a difference between the test and the reference product. This good tolerability of the test product Epoetin STADA was confirmed in the open follow-up extension period.

CONCLUSIONS

The trial was performed according to protocol, to amendment 01, and to clarification letters 01-02.
The statistical evaluation of the primary and secondary endpoints demonstrated that the test product (Epoetin STADA) is equivalent with the reference product (Erypo®) in respect of its clinical efficacy.

The evaluation of safety parameters (adverse events, occurrence of anti-epoetin antibodies, safety / special laboratory examination, rating of tolerability, and incidence of haemoglobin levels above 13 g/dl) provides no evidence for any safety concern after subcutaneous administration of Epoetin STADA.

The long-term subcutaneous treatment with Epoetin STADA for a period of at least one year is not associated with an increased risk for the patients.

Date of Final Study Report (Final Version 1.0): 13-Aug-2010

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AMENDMENT 01

INTRODUCING AN OPEN FOLLOW-UP EXTENSION PERIOD TO STUDY PROTOCOL

Study title	**Evaluation of the Therapeutic Equivalence of Two Different Formulations Containing Epoetin (Epoetin STADA vs. Erypo®) Administered Subcutaneously for the Maintenance Treatment of Renal Anaemia**	
Date of protocol	**Final version 1.0, dated 20-Jun-2007**	
Date of amendment 01	**17-Jun-2008**	
Study code	**(CRO)**	**411-54-07-08-0000**
Study number	**(Sponsor)**	**CT-830-07-0047**
EudraCT Number		**2007-002984-28**

1. Background and Rationale

As envisaged in the study protocol of the trial the present study should be continued in an open follow-up trial with the test product (subcutaneous administration of Epoetin STADA). The only objective of the present amendment is to officially introduce the follow-up period after the end of blinded treatment.

The evaluation of long-term safety data up to 1 year of Epoetin STADA administered subcutaneously to at least 200 patients with renal anaemia is part of a comprehensive Risk Management Plan and is required by the respective EMEA Guidance on Biosimilar Medicinal Products Containing Recombinant Erythropoietins (EMEA/CHMP/94526/2005) and by the EMEA Follow-Up Scientific Advice for Epoetin STADA (EMEA/CHMP/SAWP/155066/2007).

Furthermore, the sponsor's Quality Management representative will be added to the "Study administrative structure details".

This amendment introduces no changes in the study medication or in any study-related procedures. Due to this reason the overall benefit-risk evaluation of the present trial remains unchanged.

2. Scope of Amendment

The Amendment 01 refers to the Study Protocol (Final Version 1.0, dated 20-Jun-2007).

The present clinical trial comprises a 28 weeks verum-controlled main study phase, preceded by an open run-in period of 12-16 weeks with Epoetin STADA. At the end of the main study phase approximately half of all randomised patients will have been treated consecutively with Epoetin STADA for 40 weeks.

In order to fulfil the recommendations of the above-mentioned EMEA guidance and scientific advice (supply and evaluation of 1 year safety data for at least 200 patients) treatment with the test product will be continued in an open follow-up extension period. The duration of this extension period will depend on the number of patients who will start the period:

- If a sufficient number of patients (more than 200), consecutively treated with Epoetin STADA, starts the follow-up extension period of the trial and reaches at least 12 weeks of treatment in the follow-up period also providing samples for the evaluation of antibodies against epoetin the trial will be regularly completed for all enrolled patients after the last patient completes the 12 weeks treatment follow-up treatment.
- If less than 200 patients, consecutively treated with Epoetin STADA, will start follow-up treatment the duration of follow-up extension period will be 54 weeks for all patients. By following this procedure all patients who complete the follow-up extension period can be taken into consideration for the evaluation of 1 year safety data (also including these patients who were treated with the reference medication in the main study phase).

The study procedures described in the study protocol of the trial will be identical for the open follow-up extension period, with the only exception of the intervals between the visits which will be 6 weeks instead of 4 weeks. The resulting new flow chart of the follow-up extension period is presented below (chapter 3).

Due to the above-mentioned changes an additional case report form (CRF) covering the follow-up extension period (at least 12 weeks, maximum duration 54 weeks) will be prepared as well as a new information for patients/informed consent form.

Furthermore the study administrative structure will be amended with the sponsor's representative for Quality Management (chapter 1.4, page 7 of Study Protocol, Final Version 1.0):

Quality Management:

Amendment 01 prolongs the total duration of subcutaneous treatment with Epoetin STADA without introducing any changes in other study procedures related to the well-being of the patients enrolled. Due to this reason the overall benefit-risk evaluation of the trial is not changed by the present amendment.

Amendment 01 will be presented to the local ethics committees and national authorities of all countries involved for approval.

Appendix 1: Additional case report form (Final Version 1.0, dated 17-Jun-2008)

Appendix 2: Information for patients/informed consent form for open follow-up extension period (Final Version 1.0, dated 17-Jun-2008)

Appendix 3: Investigator declaration for Amendment 01