2. SYNOPSIS

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 Safety and Tolerability of a Formulation Containing Epoetin (Epoetin STADA) Administered Intravenously for the Maintenance Treatment of Renal Anemia: an Open Follow-up Trial

INVESTIGATORS:

Principal Investigators:

Investigators: Germany:

Poland:

Bulgaria:

Serbia:

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STUDY CENTERS:

n=65

28 centers in Germany, 21 centers in Poland, 12 centers in Bulgaria, 4 centers in Serbia

PUBLICATION (REFERENCE):

N/A

STUDY PERIOD:		**PHASE OF DEVELOPMENT:**
date of first enrolment (start of treatment):	23-May-2005	Phase III
date of completion whole trial:	11-Jan-2008	

OBJECTIVES:

To gather data regarding the safety of Epoetin STADA (with a particular focus on the formation of anti-epoetin antibodies) when administered intravenously for maintaining the hemoglobin concentration in anemic patients with end-stage renal failure on chronic hemodialysis.

In addition supportive information regarding the efficacy of Epoetin STADA under open, non-controlled conditions should be provided.

STUDY DESIGN:

- open
- non-controlled,
- follow-up,
- multiple-dose,
- multicenter,
- phase III,
- international,
- 620 patients planned for enrollment,
- intravenous administration (1-3 times a week at the end of dialysis into the venous loop).

SUBJECTS (planned and analyzed):		
	planned for enrollment:	620
	enrolled:	745
	drop-outs:	260
	evaluated:	745 (safety population)

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CRITERIA FOR SELECTION:	**Inclusion criteria** • male or female hemodialysis patients who have completed the double-blind treatment period of the trials 411-54-04-04-0000 (CT-830-04-0002) and 411-54-04-05-0000 (CT-830-04-0003) and who are willing to continue for another 28 weeks • 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 criteria** • myelodysplastic syndrome • detectable anti-epoetin antibodies • presence of malignant tumors • pregnancy or lactation period in female patients • severe physical or mental concomitant diseases that might hamper the realization of the trial according to protocol or the evaluation of safety or efficacy • 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: batch no.: <u>1000 IU</u> batches; expiry dates: <u>2000 IU</u> batches; expiry dates:	Epoetin STADA STADA Arzneimittel AG, Bad Vilbel, Germany 1000 or 2000 IU epoetin intravenous 1-3 times weekly
REFERENCE PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:	None	
DURATION OF TREATMENT:	108 weeks (starting without any delay after the end of the preceding double-blind treatment)	

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CRITERIA FOR EVALUATION:

Safety:

Primary endpoints:
- evaluation of adverse events,
- occurrence of anti-epoetin antibodies

Efficacy:

Secondary endpoints:
- mean weekly epoetin dosage per kg body weight,
- mean hemoglobin levels,
- mean hematocrit levels,
- proportion of patients with any permanent changes of hemoglobin levels of more than 1 g/dl,
- proportion of patients with any transient changes of hemoglobin levels of more than 1 g/dl,
- proportion of patients with any permanent dose change,
- proportion of patients with any transient dose change,
- proportion of patients with any hemoglobin measurement outside the target range,
- incidence of blood transfusions.

STATISTICAL METHODS:

The primary aim of the present trial was to provide information regarding the determination of the safety profile after intravenous administration of the test product as well as the potential for formation of anti-epoetin antibodies. The current experience from other registered formulations which contain human recombinant epoetin shows that the incidence of the target event (pure red cell aplasia due to inactivating antibodies) is extremely low (approximately 5/100,000). Taking this into account the probability to observe even one single case of antibodies in the present trial was very low.

The statistical analysis of the results of the present trial was only descriptive. Depending on their distribution the target parameters were presented with their means, SD, SEM, median and quartiles or with their incidence. No statistical comparison was possible due to the design of the trial.

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RESULTS:

The results described are presented for the FAS (full analysis set of safety) population and include data of 745 patients. The Bulgarian patients who started a second prolongation period (n=164) were examined as a subgroup for the evaluation of efficacy data.

Disposition of patients:

A total number of 745 male and female patients with end-stage renal failure on chronic hemodialysis who had completed the double-blind treatment period of the trials 411-54-04-04-0000 (CT-830-04-0002) and 411-54-04-05-0000 (CT-830-04-0003) gave their informed consent to participate in this follow-up trial in written form and were enrolled after checking of inclusion and exclusion criteria. All patients were taken into consideration for the current evaluation. The patients were enrolled in a total number of 65 centers in Germany, Bulgaria, Poland, and Serbia.

Efficacy:

Receiving supportive information regarding the efficacy of Epoetin STADA under open, non-controlled conditions was defined as a secondary objective in the present trial. For this purpose following secondary endpoints were chosen:

- mean weekly epoetin dosage per kg body weight,
- mean hemoglobin levels,
- mean hematocrit levels,
- proportion of patients with any permanent changes of hemoglobin levels of more than 1 g/dl,
- proportion of patients with any transient changes of hemoglobin levels of more than 1 g/dl,
- proportion of patients with any permanent dose change,
- proportion of patients with any transient dose change,
- proportion of patients with any hemoglobin measurement outside the target range,
- incidence of blood transfusions.

The mean weekly epoetin dosage per kg body weight and the mean hemoglobin levels are the most important secondary endpoints. The results of both endpoints are presented in TF 1 and TF 2. The graphical presentations demonstrate that Epoetin STADA is effective regarding its ability to maintain hemoglobin levels within the target range of 10.5 - 12.5 g/dl. Both figures show that the Hb values remained stable within the range between 11.3 and 11.6 g/dl until the end of the second part of the follow-up trial for the FAS population (n=745) and between 11.1 and 11.6 g/dl until the end of the whole follow-up trial for the Bulgarian subgroup (n=164) who started second prolongation period. The dosage of epoetin remained stable in the course of the trial. The dosage in the Bulgarian patients who started the second prolongation period was somewhat higher as compared to the remaining patients but it was higher from the beginning of follow-up treatment and also remained constant during the entire course of treatment. No case of lack of efficacy was observed in the course of the trial.

The results of the other secondary endpoints confirmed the results obtained for epoetin dosage and hemoglobin levels.

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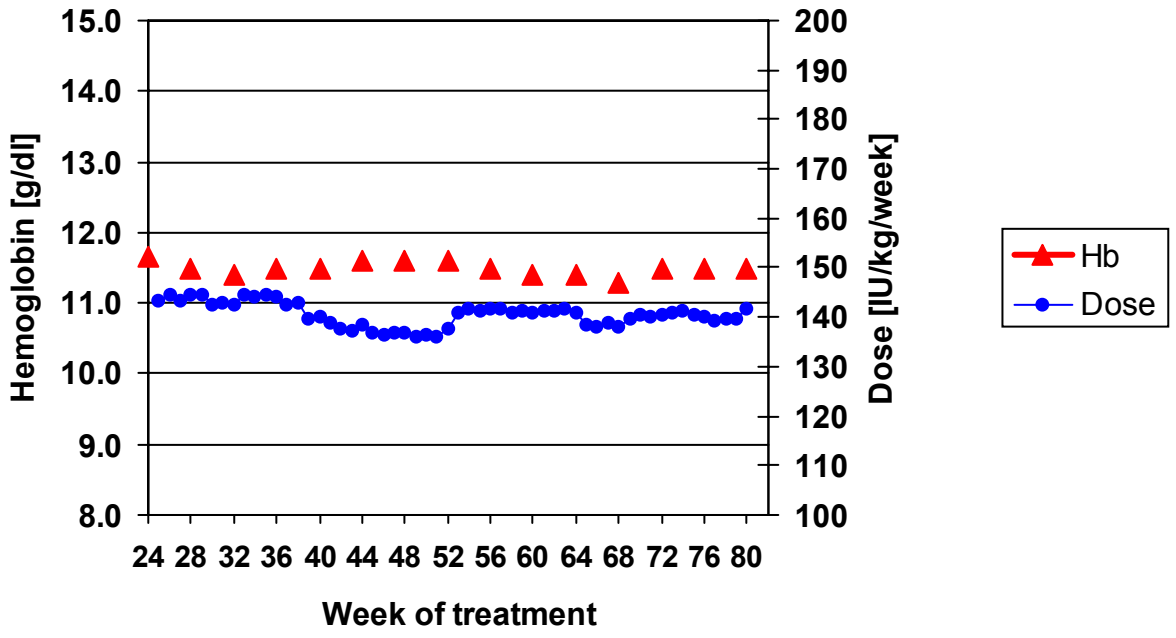

TF 1 **Hemoglobin levels vs. erythropoietin dosage (n=745)**

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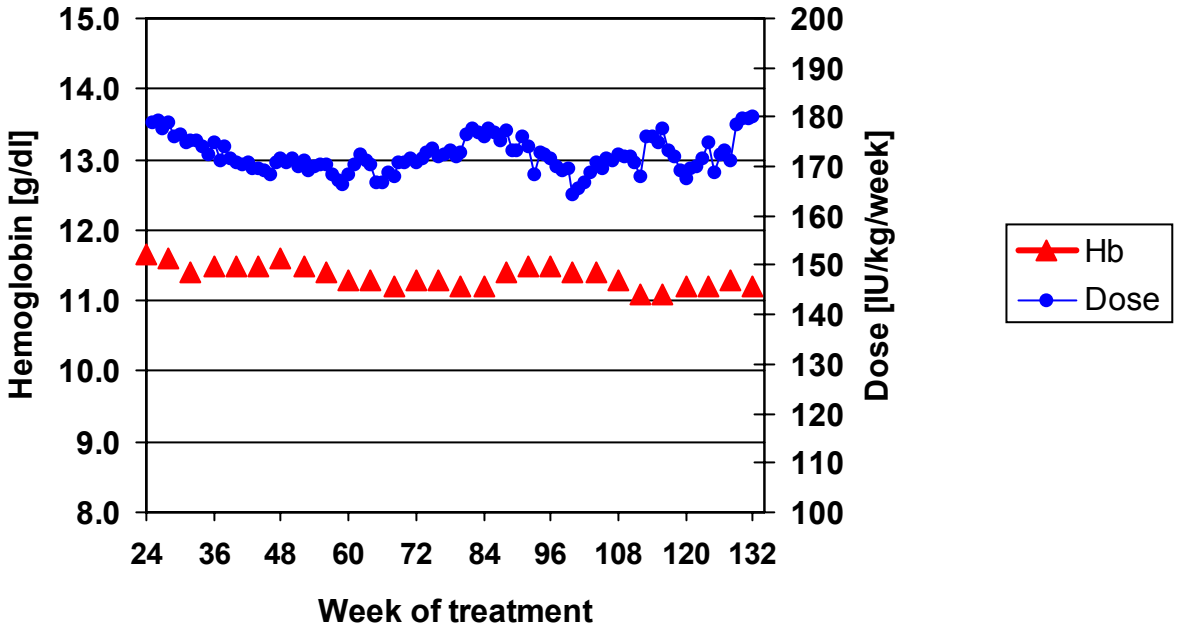

TF 2 **Hemoglobin levels vs. erythropoietin dosage for Bulgarian patients who started 2nd prolongation period (n=164)**

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Safety:

Deaths

A total number of 73 patients died in the course of the trial. These patients experienced 154 serious adverse events, which belonged mainly to the group of *nervous system disorders* and *cardiac disorders*, followed by *general disorders and administration site conditions*, *infections and infestations* and *vascular disorders*. Only in four cases, two Bulgarian patients (pat. #1040 and #1161), one Polish (#315) and one Serbian patient (#1437) the relationship between Epoetin STADA and the serious adverse events were assessed as possible by the investigators. The Bulgarian patient #1040 died due to ischemic stroke; the patient #1161 died due to hemorrhagic stroke, hemiplegia, central nervous system lesion, brain edema and cardiopulmonary failure; the Polish patient #315 died due to pneumonia, sepsis, cerebrovascular insufficiency, cardiac failure, cardiac arrest, hepatic cirrhosis, multi-organ failure and overdose of sedatives; and the Serbian patient #1437 died due to shock, hepatosplenomegaly, jaundice and secondary anemia.

Adverse events and serious adverse events

A total number of 539 patients experienced 2574 adverse events; 715 adverse events in 278 patients were serious. The majority of serious adverse events observed belonged to the group of *cardiac disorders* (112 SAEs in 64 patients), followed by *injury, poisoning and procedural complications* (80 SAEs in 52 patients), and *vascular disorders* (72 SAEs in 49 patients), as well as *infections and infestations* (70 SAEs in 57 patients), *nervous system disorders* (70 SAEs in 41 patients), *gastrointestinal disorders* (67 SAEs in 43 patients) and *surgical and medical procedures* (67 SAEs in 60 patients). In this respect the pattern of serious adverse events is comparable with data known for already registered epoetin products and with the results of the double-blind part of both preceding trials.

Anti-epoetin antibodies

All patients were tested for the presence of anti-epoetin antibodies. No case of pure red cell aplasia (PRCA) or an indication for neutralizing anti-epoetin antibodies was found. In two patients positive results for anti-epoetin antibodies were noted, but these patients were already tested positive at screening visit of the preceding clinical trial 411-54-04-05-0000 (CT-830-04-0003). A relationship between the occurrence of anti-epoetin antibodies and the use of Epoetin STADA could therefore be ruled out.

Ratings of tolerability

Epoetin STADA showed a very good overall tolerability.

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CONCLUSIONS:

The trial was performed according to protocol, amendments 01-03, and to clarification letter 01.

The evaluation of the efficacy parameters (secondary endpoints) demonstrated that Epoetin STADA is effective regarding its ability to maintain stabilized hemoglobin levels within the target range of 10.5 - 12.5 g/dl with a stable dose of the study drug.

The evaluation of the primary endpoints (adverse events, occurrence of anti-epoetin antibodies, safety/special laboratory examination, and rating of tolerability) provide no evidence for any safety concern after long-term intravenous administration of Epoetin STADA.

The results of the follow-up trial confirmed the results obtained from the preceding clinical trials 411-54-04-04-0000 (CT-830-04-0002) and 411-54-04-05-0000 (CT-830-04-0003) regarding both efficacy and safety of Epoetin STADA.

DATE OF FINAL STUDY REPORT (Final Version 1.0):
03-Apr-2008