SYNOPSIS

Name of Company: Fresenius Kabi	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: Voluven® Fresenius 6% Solution for Infusion	Volume:	
Name of Active Ingredient: Poly(O-2-hydroxyethyl)starch	Page:	
Title of Study: Crystalloids or colloids in patients with severe sepsis: effects on hemodynamics and tolerability of enteral nutrition Short title: CRYSTMAS (CRYSTalloids Morbidity Associated with severe Sepsis)		
Investigators:	Principal investigator/ Coordinating investigator and Clinical Study Centre 1:	[redacted] Service de Réanimation Médicale Hôpital St Antoine 184, rue du Faubourg St Antoine 75012 Paris, France [redacted]
	Local German Coordinating Investigator ('Leiter der klinischen Prüfung' according to German Drug Law) and investigator at Clinical Study Centre 50:	[redacted] Klinik und Poliklinik für Anästhesiologie und operative Intensivmedizin der Westfälischen Wilhelms-Universität Albert-Schweitzer-Str. 33 48149 Münster, Germany [redacted]
[redacted]	[redacted]	
Publication (reference):	Guidet B, Martinet O, Boulain T, et al. Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 versus 0.9% NaCl fluid replacement in patients with severe sepsis: The CRYSTMAS study. Crit Care 2012; 16(3):R94	
Studied period	21 July 2007 – 20 May 2010	
Phase of development	France: 3b; Germany: 4	
Objectives:	Compare haemodynamics in patients suffering from severe sepsis who have received vascular filling with Voluven® or NaCl 0.9%. Comparison between the two groups was based on the amount of study drug (mL) required to achieve the initial Haemodynamic Stabilisation (HDS). For further details please	

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	refer to primary efficacy variable below.
Methodology:	Randomised, comparative, prospective, multicentre, double-blind study
Number of patients (planned and analysed):	Planned: 180 (2 x 90) patients. Randomized & Treated: 196 patients (Treated Population (TRT); Intention-To-Treat Population (ITT)); 174 patients (Full Analysis Set, FAS).
Diagnosis and main criteria for inclusion:	Patients aged ≥18 years, with present severe sepsis and requirement for fluid resuscitation.
Test product, dose and mode of administration, and batch number:	Voluven® was infused intravenously according to individual needs and in addition according to predefined haemodynamic goals of fluid administration. [redacted] Batch numbers: UKL031, 13BGU092, 13BLL251
Duration of treatment:	Study drug was infused for up to four consecutive days.
Reference therapy, dose and mode of administration, batch number:	The reference therapy was Sodium Chloride Fresenius 0.9%. The reference therapy was to be administered in the same way as the test product. Batch numbers: UKL041, 13BGU073, 13BLL261
Criteria for evaluation: Efficacy:	**Primary efficacy variable:** Amount of study drug (mL) required to achieve initial hemodynamic stabilization [HDS; defined as normalisation of Mean Arterial Pressure and at least two of the three parameters Central Venous Pressure, Urine Output and Central Venous Oxygen Saturation that is maintained for four hours, with no increase in the infusion of vasopressors, or inotropic therapy, and with ≤ 1 L of additional study drug administration within these four hours; initial HDS was considered to be achieved at the end of this four hour period]. **Secondary efficacy variables:** Time from start of fluid resuscitation with study drug to the initial HDS, total quantity of study drug infused over four consecutive days on the Intensive Care Unit (ICU), time from start of study drug to start of Enteral Nutrition (EN) (subgroup of patients who received EN), total amount of calories received from EN over seven days (subgroup of patients who received EN), achievement of 80 % of the theoretical (prescribed) calorie intake from EN (subgroup of patients who received EN) on day 8, lengths of stay in ICU and hospital, Area Under the Curve (AUC) of Sepsis-Related Organ Failure Assessment

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	(SOFA) score from Screening to Day 4
Safety:	Tolerance to volume expansion as assessed by the investigator, coagulation parameters, fluid input, total fluid output, fluid balance, volume of Red Blood Cell (RBC) transfusions, number of RBC transfusions, number of patients with RBC transfusions, SOFA component scores, renal dysfunction at study inclusion, incidence of acute renal failure (ARF), incidence of oliguria, incidence of itching, symptoms of gastrointestinal intolerance, volume of gastric residue, vital signs, haemodynamic parameters, urine output, arterial blood gases, haematology, clinical chemistry, biomarkers of Acute Kidney Injury (AKI) and urinary creatinine, Adverse Events (AEs), mortality, physical examination results, Simplified Acute Physiology Score II (SAPS II), days on renal replacement therapy (RRT), body weight [redacted]
Statistical Methods:	The amount of study drug required to achieve the initial HDS (primary efficacy endpoint) was tested in a confirmatory sense. [redacted]
Summary - conclusions Efficacy results:	A total of 196 patients (Voluven®: 100; NaCl: 96) were randomised and treated with study drug. Statistically significant superiority of Voluven® compared to NaCl with respect to the **primary variable** was shown in the FAS at a significance level of 2.5 % one-sided (p=0.0185). The mean amount of study drug required to achieve HDS was 1379 mL in the Voluven® group and 1709 mL in the NaCl group. The observed mean difference between treatment groups was 331 mL. The 95 % confidence interval for the treatment difference was from -640 mL to -21 mL, lying completely below zero. A maximum amount of study drug of 5000 mL was administered in both treatment groups. These results, based on the FAS, were supported by analyses based on ITT, TRT, and Per-Protocol Population (PP). Based on the FAS, the mean **time from start of study drug to**

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	initial HDS was 11.8 hours in the Voluven® group (with a Standard Deviation (SD) of 10.1 hours) and 14.3 hours in the NaCl group (SD 11.1 hours). Results were similar in the PP. Based on the FAS, the **quantity of study drug over four consecutive days on the ICU** was 2615 mL in the Voluven® group (with a SD of 1499 mL) and 2788 mL in the NaCl group (SD 1799 mL). Values ranged from 500 mL to 9000 mL in both treatment groups. Results were similar in the PP. Based on the EN subgroup of the FAS, the mean **time from start of study drug to start of EN** was 24.6 hours in the Voluven® group (with a SD of 32.7 hours) and 26.9 hours in the NaCl group (SD 33.8 hours). Values ranged from 0 hours to 166.0 hours in the Voluven® group and from 0 hours to 161.8 hours in the NaCl group. Based on the EN subgroup of the FAS, the **total amount of enteral calories received during the first seven days of EN** was 6877 kcal in the Voluven® group (with a SD of 5008 kcal) and 7429 kcal in the NaCl group (SD 4381 kcal). Results were similar in the EN subgroup of the PP. Based on the EN subgroup of the FAS, ten patients (16.1 %) in the Voluven® group and seven patients (10.4 %) in the NaCl group received **80 % or more of the theoretical (prescribed) calorie intake (30 kcal/kg/day) from EN**. Twenty-five patients (40.3 %) in the Voluven® group and 36 patients (53.7 %) in the NaCl group received **50 % or more of the theoretical (prescribed) calorie intake (30 kcal/kg/day) from EN**. **Length of stay in ICU** and **length of stay in hospital** were comparable in both treatment groups. Based on the FAS, the mean **AUC of the SOFA score per day from Screening to Day 4** was 6.9 in the Voluven® group (with a SD of 3.3) and 7.6 in the NaCl group (SD 3.1). Results were similar in the PP.
Safety results:	In general, Voluven® was well tolerated in this study, with many of the most commonly reported AEs being symptoms related to the underlying sepsis disease. Overall, treatment emergent **AEs** and **ADRs** were experienced by comparable numbers of patients in each treatment group.

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Treatment groups were comparable with regard to the overall frequency of renal and urinary disorders (26.0 % in the Voluven® group vs. 19.8 % in the NaCl group). The **AKIN** and **RIFLE** classifications of patients were comparable among both treatment groups, with no statistically significant difference being detected (in an exploratory sense). The results from **biomarker analyses** suggested that Voluven® did not induce AKI.

The number of patients with an indication for or actually receiving renal replacement therapy was not significantly different (p=0.18; p=0.07).

The **mortality rate** was not statistically significant different (in an exploratory sense) between treatments. Serious Adverse Events (SAEs) leading to death were observed in 40 patients (40.0 %) in the Voluven® group and 32 patients (33.3 %) in the NaCl group. None of the fatal SAEs were considered to be related to study drug. Most of the fatal SAEs, other SAEs and events leading to discontinuation of study drug were complications from severe infection and underlying disease. The pattern and frequency of these events was comparable between treatment groups.

No difference between the treatment groups was considered clinically significant for any **laboratory parameter** (including urine output and coagulation parameters). Although not considered clinically relevant, median change of **platelet count** from baseline was different between treatments. In particular, there was no statistically significant treatment difference (in an exploratory sense) in median change of serum creatinine from baseline or peak post-baseline serum creatinine. Moreover, no clinically relevant differences between treatment groups were observed with respect to mean serum creatinine and mean urea over the study course. Creatinine and urea shift tables from baseline showed lower frequencies of change to high for patients in the Voluven® group. Furthermore, the frequency of patients with elevated serum creatinine at baseline and at any post-baseline time point was comparable between groups; no statistically significant difference (in an exploratory sense) was detected. For **ARF** no statistically significant difference (in an

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	exploratory sense) was found between treatments. Study drugs were not identified as statistically significant risk factors of ARF (in an exploratory sense). There were no clinically significant differences between the treatment groups for any vital signs parameter or haemodynamic parameter. Tolerance to volume expansion also was similar between treatments. Given the type of disease investigated in this study (severe sepsis), there were no unexpected shifts in physical examination.
Conclusion:	In summary, Voluven® was significantly superior to NaCl with respect to the amount of study drug required to achieve initial HDS, and there was no difference between treatment groups regarding the frequency of patients not achieving HDS. Voluven® was generally well tolerated by patients with severe sepsis. The clinical trial indicated that for patients suffering from severe sepsis the administration of the colloid Voluven® is associated with a favourable outcome regarding the primary efficacy parameter.