## SYNOPSIS

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| Name of Company:<br>Fresenius Kabi | Individual Study Table Referring to Part of the Dossier | (For National Authority Use only) |
| Name of Finished Product:<br>Voluven® Fresenius 6% Solution for Infusion | Volume: | |
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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)

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| Investigators: | Principal investigator and Clinical Study Centre 1: | Prof. Bertrand Guidet<br>Service de Réanimation Médicale<br>Hôpital St Antoine<br>184, rue du Faubourg St Antoine<br>75012 Paris, France |
| | Investigator at Clinical Study Centre 2: | Dr. Gérard Audibert<br>Service Anesthésie-Réanimation Chirurgicale<br>CHU - Hôpital Central<br>29 av du Mal de Lattre de Tassigny<br>54035 Nancy, France |
| | Investigator at Clinical Study Centre 3:<br><br>(no patients enrolled) | Prof. Gilles Bernardin<br>CHU Nice - Hôpital Archet<br>Service de Réanimation Médicale<br>151 route Saint-Antoine de Ginestière<br>06202 Nice, France |

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| Investigator at Clinical Study Centre 4: | Dr. Pascal Beuret<br>CH Roanne<br>Service de Réanimation<br>28 rue de Charlieu<br>42328 Roanne Cedex, France |
| Investigator at Clinical Study Centre 5: | Dr. Thierry Boulain<br>Hôpital de la Source<br>Réanimation Polyvalente<br>1, rue Porte Madeleine<br>45032 Orléans, France |
| Investigator at Clinical Study Centre 6: | Prof. Yves Cohen<br>Hôpital Avicenne<br>Service de Réanimation<br>125 route de Stalingrad<br>93009 Bobigny, France |
| Investigator at Clinical Study Centre 7: | Prof. Jacques Duranteau<br>CHU de Bicêtre<br>Dpt d'Anesthésie Réanimation Chir<br>78, rue du Général Leclerc<br>94275 Le Kremlin-Bicêtre, France |

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| Investigator at Clinical Study Centre 8: | Dr. Marc Feissel<br>Centre Hospitalier de Belfort-Montbéliard<br>Service de Réanimation et Maladies Infectieuses<br>Site de Belfort<br>14, rue de Mulhouse<br>90000 Belfort, France |
| Investigator at Clinical Study Centre 9: | Prof. Michel Hasselman<br>Hôpital Civil de Strasbourg<br>Service de Réanimation Médicale<br>Place de l'Hôpital<br>67091 Strasbourg, France |
| Investigator at Clinical Study Centre 10: | Prof. Laurent Jacob<br>Hôpital St Louis<br>Département Anesthésie et Réanimation Chirurgicale 1er étage<br>1 rue Claude Vellefaux<br>75010 Paris, France |

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| Investigator at Clinical Study Centre 11:<br><br>(no patients enrolled) | Prof. Gérard Janvier<br>CHU Bordeaux<br>Groupe Hospitalier Sud<br>Département d'Anesthésie Réanimation Chirurgicale II<br>Avenue du Haut-Lévêque<br>33604 Pessac, France |
| Investigator at Clinical Study Centre 12: | Dr. Pascal Meyer<br>CH Sud Francilien<br>Site Gilles de Corbeil<br>Réanimation Polyvalente<br>59 Bd Dunant<br>91106 Corbeil-Essonnes Cedex, France |
| Investigator at Clinical Study Centre 13:<br><br>(no patients enrolled) | Dr. Pierre Michelet<br>Hôpital Ste Marguerite<br>Dpt d'Anesthésie-Réanimation<br>270 Bd Ste Marguerite<br>13200 Marseille, France |

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| Investigator at Clinical Study Centre 14: | Dr. Benoît Misset<br>Hôpital Saint-Joseph<br>Service de Réanimation Polyvalente<br>185, rue Raymond Losserand<br>75014 Paris, France |
| Investigator at Clinical Study Centre 15: | Dr. Laurent Muller<br>Service de Réanimation<br>Division Anesthésie-Réa Douleur Urgence<br>Groupe Hospitalo-Universitaire Caremeau<br>CHU Nîmes<br>Place du Pr Robert Debré<br>30029 Nîmes cedex, France |
| Investigator at Clinical Study Centre 17:<br><br>(no patients enrolled) | Dr. Gaëtan Plantefève<br>Centre Hospitalier Victor Dupouy<br>Urgences et Réanimation<br>69 rue du Ltnt Colonel Prudhon,<br>95107 Argenteuil, France |
| Investigator at Clinical Study Centre 18: | Dr. Jean François Poussel<br>Centre Hospitalier de Metz<br>Réa Polyvalente<br>1 place Philippe de Vigneulles<br>57038 Metz cedex, France |

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| Investigator at Clinical Study Centre 19: | Dr. Jean-Pierre Quenot<br>CHU de Dijon - Hôpital du Bocage Service de Réanimation Médicale<br>2 Bld du Mal de Lattre de Tassigny<br>21079 Dijon cedex, France |
| Investigator at Clinical Study Centre 20: | Dr. Jean-Louis Ricome<br>CHI Poissy - St Germain en Laye<br>Site de St Germain en Laye<br>20 rue Armagis<br>Réanimation Médico-chirurgicale<br>78100 St Germain en Laye, France |
| Investigator at Clinical Study Centre 21: | Prof. Michel Slama<br>Hôpital Sud<br>Unité de Réanimation Médicale<br>Avenue René Laënnec-Salouël<br>80054 Amiens, France |
| Investigator at Clinical Study Centre 22:<br><br>(no patients enrolled) | Prof. Jean-Claude Zeni<br>CHU St Etienne - Hôpital Nord<br>Service de Réanimation Médicale et Polyvalente<br>Avenue Albert Raimond<br>42270 Saint-Priest en Jarez, France |

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| Investigator at Clinical Study Centre 23:<br><br>(no patients enrolled) | Dr. Nicolas Boussekey<br>Service de Réanimation Médicale et Infectieuse<br>135 rue du Président Coty<br>59208 Tourcoing, France |
| Investigator at Clinical Study Centre 24: | Prof. Xavier Capdevila<br>Hôpital Lapeyronie / CHU Montpellier<br>Département d'Anesthésie Réanimation A<br>371 avenue du Doyen Gaston Giraud<br>34090 Montpellier Cedex 5, France |
| Investigator at Clinical Study Centre 25: | Dr. Karim Debbat<br>Service de Réanimation Polyvalente<br>Centre Hospitalier d'Avignon<br>305 rue Raoul Follereau<br>84902 Avignon Cedex 9, France |
| Investigator at Clinical Study Centre 26: | Prof. Bernard Just<br>Service de Réanimation Polyvalente CH Manchester<br>45 avenue Manchester<br>08011 Charleville-Mézières, France |

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| Investigator at Clinical Study Centre 27:<br><br>(no patients enrolled) | Dr. Khaldoun Kuteifan<br>Service de Réanimation Médicale Hôpital Emile Muller<br>20, avenue du Docteur René Laënnec<br>68100 Mulhouse cedex, France |
| Investigator at Clinical Study Centre 29: | Dr. Xavier Tchenio<br>Service de Réanimation Polyvalente Centre Hospitalier Fleyriat<br>900 route de Paris<br>01012 Bourg-en-Bresse cedex, France |
| Investigator at Clinical Study Centre 31:<br><br>(no patients enrolled) | Prof. Jean-Pierre Dupeyron<br>Département d'Anesthésie Réanimation Hôpital Civil<br>1 place de l'Hôpital<br>67000 Strasbourg, France |
| Investigator at Clinical Study Centre 32:<br><br>(no patients enrolled) | Dr. Jean-Marc Boyer<br>Service de Réanimation Polyvalente CH de Laval<br>Rue du Haut Rocher<br>53015 Laval, France |

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| Investigator at Clinical Study Centre 33:<br><br>(no patients enrolled) | Dr. Michel Bemer<br>Service de Réanimation<br>CHR Bel Air<br>1-3 rue du Friscaty<br>57126 Thionville, France |
| Investigator at Clinical Study Centre 34: | Dr. Xavier Forceville<br>Service de Réanimation<br>CH Meaux<br>6-8, rue Saint-Fiacre<br>77104 Meaux, France |
| Investigator at Clinical Study Centre 50: | Prof. Dr. med. Hugo Van Aken<br>Klinik und Poliklinik für Anästhesiologie und operative Intensivmedizin der Westfälischen Wilhelms-Universität<br>Albert-Schweitzer-Str. 33<br>48149 Münster, Germany |

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| Investigator at Clinical Study Centre 52:<br><br>(no patients enrolled) | Dr. med. Ulrich Jaschinski<br>Klinikum Augsburg<br>Klinik für Anästhesie und Operative Intensivmedizin<br>Abteilungsbüro 3A<br>Stenglinstr. 2<br>86156 Augsburg, Germany |
| Investigator at Clinical Study Centre 53: | Prof. Dr. med. Udo Kaisers<br>Klinik und Poliklinik für Anästhesiologie und Intensivtherapie<br>Universitätsklinikum Leipzig AöR<br>Liebigstraße 20<br>04103 Leipzig, Germany |
| Investigator at Clinical Study Centre 54:<br><br>(no patients enrolled) | PD Dr. med. Gerhard Kuhnle<br>Universitätsklinikum Hamburg Eppendorf<br>Klinik und Poliklinik für Anästhesiologie<br>Martinistr. 52<br>20246 Hamburg, Germany |

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| | Investigator at Clinical Study Centre 55:<br><br>(no patients enrolled) | Prof. Dr. med. Maximilian Ragaller<br>Klinik und Poliklinik für Anästhesiologie und Intensivtherapie<br>Universitätsklinikum Dresden<br>Fetscherstraße 74<br>01307 Dresden, Germany |
| | Investigator at Clinical Study Centre 56:<br><br>(no patients enrolled) | Prof. Dr. med. Norbert Roewer<br>Klinik und Poliklinik für Anästhesiologie<br>Universitätsklinikum Würzburg<br>Zentrum Operative Medizin<br>Oberdürrbacher Straße 6<br>97080 Würzburg, Germany |
| | Investigator at Clinical Study Centre 57: | Prof. Dr. med. Klaus Unertl<br>Universitätsklinikum Tübingen<br>Klinik für Anästhesiologie und Intensivmedizin<br>Hoppe-Seyler-Straße 3<br>72076 Tübingen, Germany |
| Sub-investigators: | For details, see Appendix 16.1.4 | |

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| Publication (reference): | Not applicable |
| Studied period | 21 July 2007 (first patient enrolled) to 20 May 2010 (follow-up of last patient completed) |
| Phase of development | France: 3b<br>Germany: 4 |
| Objectives: | The primary objective was to compare haemodynamics in patients suffering from severe sepsis who have received vascular filling with Voluven® (colloid treatment group) or NaCl 0.9% (crystalloid control group). Comparison between the two groups was based on the amount of study drug (mL) required to achieve the initial Haemodynamic Stabilisation (HDS, defined as normalisation of Mean Arterial Pressure (MAP) and at least two of the three parameters Central Venous Pressure (CVP), urine output and Central Venous Oxygen Saturation ($ScvO_2$) 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).<br><br>The secondary objectives were to explore the efficacy of Voluven® compared to NaCl 0.9% with respect to the following variables:<br>• Time taken to achieve the initial HDS<br>• Total quantity of study drug infused over four consecutive days on the Intensive Care Unit (ICU)<br>• Time to start of Enteral Nutrition (EN) (subgroup of patients who received EN)<br>• Total amount of calories received from EN over seven days (subgroup of patients who received EN) |

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| | • Achievement of 80 % of the theoretical (prescribed) calorie intake from EN (subgroup of patients who received EN)<br>• Lengths of stay in ICU and hospital<br>• Area Under the Curve (AUC) of Sepsis-Related Organ Failure Assessment (SOFA) score from Screening to Day 4 |
| Methodology: | Randomised, comparative, prospective, multicentre, double-blind study |
| Number of patients (planned and analysed): | 180 (2 x 90) patients had been planned to be randomised according to the original CSP. After CSP Amendment 3.0, 90 patients per group were planned to be randomised after implementation of this amendment, additionally to the patients randomised before its implementation (Total: 196 patients). 196 patients were randomised and treated and analysed for safety analysis (Treated Population (TRT)) and exploratory efficacy analysis (Intention-To-Treat Population (ITT)), 100 patients in the Voluven® group and 96 patients in the NaCl group. Twenty-two patients did not reach HDS and were excluded from the Full Analysis Set (FAS) population. Thus, 174 patients (FAS) were analysed for confirmatory efficacy analysis (88 patients in the Voluven® group and 86 patients in the NaCl group). |
| Diagnosis and main criteria for inclusion: | Patients aged 18 years or over, with present severe sepsis and requirement for fluid resuscitation. |
| Test product, dose and mode of administration, and batch number: | The test product was Voluven®, solution for infusion, containing the synthetic colloid Hydroxyethyl Starch (HES) in isotonic sodium chloride (0.9%) solution. It was provided in sterile 500 mL Polyvinyl Chloride (PVC) bags for France and in sterile 500 mL polyolefine (freeflex®) bags for Germany. After randomisation, the test product |

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| | was infused intravenously according to individual needs and in addition according to predefined haemodynamic goals of fluid administration. Administration of the test product was allowed for up to four consecutive days, up to 50 mL/kg on the first day, and up to 25 mL/kg/day on the second, third, or fourth day of administration. A total of 10 000 mL of the test product were available for each patient.<br>Batch numbers: UKL031, 13BGU092, 13BLL251 | |
| Duration of treatment: | Study drug was used for fluid resuscitation, following randomisation, according to individual needs and in addition according to predefined haemodynamic goals of fluid administration, 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.<br>Batch numbers: UKL041, 13BGU073, 13BLL261 | |
| Criteria for evaluation:<br>Efficacy: | **Primary efficacy variable:**<br>• Amount of study drug (mL) required to achieve initial HDS.<br>**Secondary efficacy variables:**<br>• Time from start of fluid resuscitation with study drug to the initial HDS<br>• Total quantity of study drug infused over four consecutive days on the ICU<br>• Time from start of fluid resuscitation with study drug to start of EN<br>• Time from start of fluid resuscitation with study drug to start of EN after HDS<br>• Total amount of enteral calories during the first seven days of EN<br>• Percentage of patients receiving at least 80 % of theoretical (prescribed) calorie | |

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| | intake (30 kcal/kg/day) from EN until 7 a.m. on Day 8.<br>• Lengths of stay in ICU<br>• Lengths of stay in hospital<br>• AUC of SOFA score per day from Screening to Day 4 | |
| Safety: | • Tolerance to volume expansion as assessed by the investigator<br>• Coagulation parameters<br>• Fluid input<br>• Total fluid output<br>• Fluid balance<br>• Volume of Red Blood Cell (RBC) transfusions from start of study medication to the end of the day after the day of last study drug administration<br>• Number of RBC transfusions from start of study medication to the end of the day after the day of last study drug administration<br>• Number of patients with RBC transfusions from start of study medication to the end of the day after the day of last study drug administration<br>• SOFA component scores<br>• Renal dysfunction at study inclusion<br>• Incidence of Acute Renal Failure (ARF)<br>• Incidence of oliguria<br>• Incidence of itching<br>• Symptoms of gastrointestinal intolerance<br>• Volume of gastric residue<br>• Coagulation<br>• Vital signs<br>• Haemodynamic parameters | |

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| | • Urine output<br>• Arterial blood gases<br>• Haematology<br>• Clinical chemistry<br>• Biomarkers of Acute Kidney Injury (AKI) and urinary creatinine<br>• Adverse Events (AEs)<br>• Mortality<br>• Physical examination results<br>• Simplified Acute Physiology Score II (SAPS II) for the 24 hours prior to randomisation<br>• Days on renal replacement therapy<br>• Body weight |
| Statistical Methods | The amount of study drug required to achieve the initial HDS (primary efficacy endpoint) was tested in a confirmatory sense using a one-sided t-test with a type I error ≤ 2.5 % one-sided.<br>All other tests were strictly explorative.<br>Pearson's $\chi^2$ test was conducted to investigate the frequency of patients who did not reach HDS, and to investigate mortality, renal dysfunction at study inclusion, ARF, oliguria, and the need for renal replacement therapy.<br>T-tests were used to further examine the primary efficacy endpoint, to examine the total amount of enteral calories received from EN, the volume of RBC transfusions, and biomarkers of AKI.<br>A forward selection Analysis of Covariance (ANCOVA) procedure was used to identify parameters with an effect on the primary efficacy endpoint.<br>A logistic regression of mortality was carried out. Forward selection logistic regressions were |

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| | conducted in order to identify independent variables with an effect on mortality and incidence of ARF.<br>Kaplan-Meier curves were constructed for survival and ARF-free survival.<br>Exploratory two-sided U-tests according to Mann-Whitney were used to investigate the length of stay in ICU, number of RBC transfusions per patient, biomarkers of AKI, serum creatinine, and peak post-baseline serum creatinine.<br>Receiver Operating Characteristic (ROC) Curves were constructed for biomarkers of AKI.<br>Fisher's exact test was used to examine the number of patients with RBC transfusions, with biomarker values above the optimal cutpoint (from ROC analysis), with elevated serum creatinine values, and with clinically relevant laboratory values.<br>A $\chi^2$-test was used to test the non-inferiority of Voluven® to NaCl regarding the risk of ARF.<br>Kolmogorov-Smirnov-Tests were carried out to test for normality of biomarker values.<br>Cochran-Mantel-Haenszel tests for trend were used to examine Acute Kidney Injury Network (AKIN) and Risk, Injury, Failure, Loss, End-Stage Kidney Disease (RIFLE) classifications.<br>Homogeneity of treatment groups was tested using Student's t-tests for continuous data and $\chi^2$-tests for categorical data.<br>F-tests of equal variances were carried out to determine whether t-tests assuming equal or unequal variances were to be applied.<br>Descriptive analyses were performed for secondary efficacy variables, safety variables, and other assessments. | |

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Summary -conclusions

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| Efficacy results: | A total of 196 patients were randomised and treated with study drug. One-hundred patients were randomised to the Voluven® group and 96 patients were randomised to the NaCl group. Overall, the treatment groups were comparable in terms of **demographics and other baseline characteristics** such as physical examination results, medical and surgical history, causative organism, and concomitant medication. A slight difference between treatment groups was observed in site of sepsis: The frequency of **intra-abdominal sepsis** was higher in the Voluven® group (24 patients (24.0 %)) than in the NaCl group (18 patients (18.8 %)), which might be important as treatment of intra-abdominal infections represents a particular challenge, primarily because of the polymicrobial nature of these infections and their association with high rates of morbidity and mortality.<br>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, using a one-sided t-test assuming unequal variances, as variances were significantly different between treatment groups). 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 |

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| | the FAS, were supported by analyses based on ITT, TRT, and Per-Protocol Population (PP).<br>Based on the FAS, the mean **time from start of study drug to 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.<br>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.<br>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.<br>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.<br>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**. | |

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| | **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. | |
| Summary - conclusions | | |
| 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.<br>Overall, treatment emergent **AEs** were experienced by comparable numbers of patients in each of the two treatment groups. Likewise, the Voluven® and NaCl groups were similar with respect to the numbers of patients who had AEs that were considered related to study drug. 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; these analyses were considered supportive). The results from **biomarker analyses** suggested that Voluven® did not induce AKI, because neither the tubular, nor the glomerular function was affected.<br>The number of patients with an indication for renal replacement therapy, whether or not having received therapy, was not significantly different (p=0.18). Similarily, there was no significant difference in the number of patients who actually | |

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received renal replacement therapy (p=0.07).
The **mortality rate** was similar between the two treatment groups; no statistically significant difference (in an exploratory sense) was found 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. Two of the deaths observed in the Voluven® group (Patient 2105 and Patient 5008) were related to non-treatment emergent SAEs (septic shock and tachyarrhythmia, respectively). None of the fatal SAEs were considered to be related to study drug. Most of the fatal SAEs were complications from severe infection and underlying disease. The same applied to other SAEs and events leading to discontinuation of study drug; the latter was uncommon. 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 over the study course (at last available measurement: -22 500 × 1/mm³ (Voluven®) vs. 52 000 × 1/mm³ (NaCl)), with absolute median values of ≥ 250 000 × 1/mm³ for both groups. 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

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| | 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. If **ARF** was formally defined as at least two-fold increase of serum creatinine from baseline and/or need for renal replacement therapy at any time during the study, no statistically significant difference (in an exploratory sense) was found between treatments. Study drugs were not identified as statistically significant risk factors of ARF (in an exploratory sense).<br>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.<br>Voluven® was generally well tolerated by patients with severe sepsis based on the frequency of treatment emergent AEs/SAEs, drug-related AEs/SAEs and events leading to discontinuation of study drug. Treatment groups were comparable with regard to AKIN and RIFLE classifications, | |

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| | with no statistically significant difference being detected (in an exploratory sense; these analyses were considered supportive). The number of patients with an indication for renal replacement therapy, whether or not having received therapy, was not significantly different. Similarily, there was no significant difference in the number of patients who actually received renal replacement therapy. This observation was paralleled by no changes in renal function parameters which were comparable between treatment groups. Treatment groups were also comparable in view of other safety evaluations. 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. | |