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: Evaluation of the efficacy of 6% hydroxyethyl starch (HES, 130/0.4) in normal saline compared to Ringer's lactate solution for the prevention of hypotension during spinal anaesthesia for caesarean section

Investigators:	Coordinating investigator and site:	[redacted] Hôpital Béclère Service Anesthésie-Réanimation 157 Rue de la Porte de Trivaux 92140 Clamart France
	Investigators and sites:	[redacted] [redacted] [redacted] Hôpital Foch, Suresnes [redacted] Hôpital Hotel Dieu, Lyon [redacted] Hôpital Jeanne de Flandre, Lille [redacted] Hôpital Cochin, Paris [redacted] Hôpital Caremeau, Nimes [redacted] Hôpital Hautepierre, Strasbourg [redacted] Hôpital Robert Debre [redacted] Hôpital de l'Archet, Nice [redacted] Hôpital Hotel Dieu, Clermont Ferrand [redacted] Hôpital Louis-Mourier, Colombes [redacted] Hôpital Armand-Trousseau, Paris [redacted] Centre Hospital-

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	Universitaire de Bicêtre, Le-Kremlin-Bicêtre
	[redacted] Hôpital Lapeyronie-Arnaud de Villeneuve, Montpellier [redacted] Maternité Paule de Viguier, Toulouse
Publication (reference):	n.a.
Studied period	24-July-2008 (first subject enrolled) to 17-December-2009 (last subject completed)
Phase of development	Phase IV
Objectives:	This study compared the clinical efficacy and safety of HES 130/0.4 (6%) in normal saline (Voluven®) vs. Ringer's lactate solution in prevention of hypotension during spinal anaesthesia for elective caesarean section. The primary objective of the study was to demonstrate superiority of HES 130/0.4 (6%) with regard to the incidence of hypotension between induction of spinal anaesthesia and delivery. Secondary parameters for exploratory analysis were defined as: Minimum systolic blood pressure until delivery, maternal heart rate, time and duration of hypotension, total phenylephrine requirements until delivery, laboratory parameters, umbilical pH, infant outcome, and Adverse Events.
Methodology:	Controlled, randomized, parallel-group, double-blind multi-centre trial
Number of patients (planned and analysed):	Planned in the protocol 158 patients (79 per treatment group). At the first planned interim analysis the sample size was increased to 303 patients with a second interim analysis after 152 patients. The study was discontinued shortly after the second interim analysis. 167 patients were enrolled and analysed for safety and efficacy. One patient was withdrawn.
Diagnosis and main criteria	Women undergoing elective caesarean section

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for inclusion:	applying spinal anaesthesia, ≥37 weeks of gestation, with singleton pregnancy. Patients should be at least 18 years old and in good health with ASA classification I or II.
Test product, dose and mode of administration, and batch number:	One bottle 6% HES 130/0.4, 500 mL, followed by one bottle Ringer's lactate solution 500 mL were administered intravenously directly before induction of anaesthesia. Batch numbers were WM3306 for Voluven® Fresenius 6% Solution for infusion and WL3308 for Ringer's lactate solution.
Duration of treatment:	Single infusion 15-30 minutes
Reference therapy, dose and mode of administration, batch number:	Two bottles, each 500 mL, Ringer's lactate solution were administered intravenously directly before induction of anaesthesia. Batch number were WL 3308 and 14CF3324.
Criteria for evaluation: Efficacy:	The primary efficacy criterion was the incidence of hypotension defined as a systolic blood pressure below 80% of baseline systolic blood pressure. Further efficacy criteria were blood pressure and heart rate until delivery, onset and duration of hypotension, phenylephrine requirements, and Apgar score of the neonate.
Safety:	Safety criteria were adverse events, clinical laboratory measurements (coagulation, haematology, clinical chemistry), vital signs, physical examination, oxygen saturation, and umbilical cord blood pH and HES concentration in umbilical cord blood.
Statistical Methods	Descriptive analyses were performed for all efficacy and safety variables. The primary efficacy criterion was analysed by means of a logistic regression. Two interim analyses were performed. The significance level was adjusted for the interim analyses by means of the methods of Bauer and Köhne (1994) and Brannath, Posch and Bauer (2002). The time to onset of hypotension was analysed by means of the

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	Kaplan-Meier estimate. Umbilical cord blood pH was analyzed by means of an analysis of variance and analysis of covariance.	
Summary conclusions Efficacy results:	A total of 167 patients were randomized, 82 to HES 130/0.4 (6%) and 85 to Ringer's lactate solution. One patient in the Ringer's lactate solution group was withdrawn prematurely due to protocol violation. All other patients completed the study. The PP population comprises 140 patients, 68 in the Voluven® group and in 72 in the Ringer's lactate solution group Hypotension occurred in 30 patients (36.6%) of the HES 130/0.4 (6%) group and in 47 patients (55.3%) of the Ringer's lactate solution group (ITT population). This difference was statistically significant (p=0.025). In the PP population, hypotension occurred in 23 patients (33.8%) of the HES 130/0.4 (6%) group and in 40 patients (55.6%) of the Ringer's lactate solution group (p=0.019). Mean minimum post-baseline systolic blood pressure was 97.8 mm Hg (Voluven®) and 93.5 mm Hg (Ringer's lactate solution). Phenylephrine requirements were lower in the mean for HES 130/0.4 (6%) (418.5 µg) than for Ringer's lactate solution (451.8 µg).	
Safety results:	Adverse events were reported for 66 patients in the HES 130/0.4 (6%) group (80.5%) and for 73 patients in the Ringer's lactate solution group (85.9%). MedDRA system organ classes occurring in more than 10% in any treatment group were injury, poisoning and procedural complications (HES 130/0.4 (6%) 64.6% of patients, Ringer's lactate solution 76.5%), skin and subcutaneous tissue disorders (HES 130/0.4 (6%) 13.4%, Ringer's lactate	

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	solution 9.4%), and infections and infestations (HES 130/0.4 (6%) 11.0%, Ringer's lactate solution 4.7%). Four patients in each group had serious adverse events. The maximal grade of adverse events was 3 (severe) in each treatment group. No SAE or AE lead to discontinuation of study drug or was related to study drug. No patient died in this study.	
Conclusion:	The incidence of hypotension was statistically significantly lower for HES 130/0.4 (6%) than for Ringer's lactate solution in the ITT-analysis (36.6 % versus 55.3 %). This result is supported by the analysis of the PP-population. The minimum systolic blood pressure was lower and onset of hypotension was earlier in the Ringer's lactate solution group. A higher number of patients in the Ringer's lactate solution group experienced severe hypotension below 70% of baseline systolic blood pressure. Phenylephrine requirement was lower in the HES 130/0.4 (6%) group. There was no difference between both treatment groups concerning duration of surgical procedures. In both treatment groups APGAR score showed the maximum achievable values both after 1 and 5 minutes. A negative influence on the neonate could not be detected. Exposure to study drug was similar in both treatment groups. The number of AEs in the Ringer's lactate solution group was slightly higher than in the HES 130/0.4 (6%) group. Procedural Nausea and procedural vomiting occurred more often in the Ringer's lactate solution group, suggesting a preventive effect of HES 130/0.4 (6%) on the occurrence of these AEs.	

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	No AEs were related to study drug. No AE with severity grade higher than 3 occurred. No AE lead to discontinuation of a patient. In four patients in each group an SAE was observed. Seven SAEs concerned the neonates. None of the SAEs were assessed as related to the study drug. No patient died during the course of the study. No clinically relevant differences in laboratory parameters and vital signs between treatment arms. Mean blood pressure values were lower in the Ringer's lactate solution group during surgery. Umbilical cord blood pH shows no difference between both treatment groups. HES could not be detected in umbilical cord blood in 6 patients receiving HES 130/0.4 (6%) as study drug. Overall efficacy evaluation showed clear benefits for HES 130/0.4 (6%) in the prevention of hypotension and in the occurrence of severe hypotension. The safety evaluation shows advantages for HES 130/0.4 (6%) regarding the occurrence of nausea and vomiting compared to Ringer's lactate solution. No negative influence of HES 130/0.4 (6%) on patient safety could be detected.	