SYNOPSIS

Name of sponsor	B. Braun Melsungen AG, Carl-Braun-Straße 1, 34212 Melsungen, Germany
Name of finished product	Tetraspan®10%
Name of active ingredient	Hydroxyethyl starch (HES) (Molar substitution: 0.42; average molecular weight: 130 000 Dalton)
Study title	Prospective, controlled, double-blind, randomized multicentric study on the efficacy and safety of a target controlled plasma volume replacement therapy with a hyper-oncotic balanced HES 130/0.42 solution vs an iso-oncotic balanced HES 130/0.42 solution compared to a balanced electrolyte solution in elective surgery of the pancreatic head
Investigators	Coordinating Investigator : Charité-Universitätsmedizin Berlin Campus Virchow-Klinikum Principal Investigator Center 1 : Charité-Universitätsmedizin Berlin Campus Virchow-Klinikum Principal Investigator Center 2 : Humboldt Klinikum Berlin Principal Investigator Center 3 : Universitätsklinikum Bonn
Study centers	1. Klinik für Anästhesiologie mit Schwerpunkt operative Intensivmedizin Charité-Universitätsmedizin Berlin Campus Virchow-Klinikum Augustenburger Platz 1 13353 Berlin, Germany 2. Klinik für Anästhesie, operative Intensivmedizin und Schmerztherapie Humboldt Klinikum Am Nordgraben 1 13509 Berlin, Germany 3. Universitätsklinikum Bonn Chirurgisches Zentrum Klinik für Anästhesiologie Sigmund-Freud-Straße 25 53127 Bonn, Germany
Publication (reference)	–
Study period	Date of first patient enrolled : 03.06.2010 Date of last patient completed*: 26.07.2012 * After inclusion of the 60 patients into the pilot phase, patient recruitment was temporary halted, for re-assessment of sample size as scheduled in the study protocol. This temporary halt was carried on for implementation of an independent data monitoring committee awaiting the recommendation about the further conduct of the study. Thus, at the time point of the decision to finally terminate the study, no further patients had been recruited.
Phase of development	IV
Objectives	Primary objective: Investigation on efficacy of target controlled fluid therapy with a hyper-oncotic balanced HES 130/0.42 solution compared to an iso-oncotic HES 130/0.42 solution in patients undergoing elective surgery of the pancreatic head. A third group receiving a balanced electrolyte solution (without colloidal volume replacement) serves as a control for descriptive analysis.

	Secondary objectives: Investigation of safety and secondary efficacy parameters of the balanced HES 130/0.42 solutions and of the balanced electrolyte solution.		
Methodology	Prospective, controlled, randomized, double-blind, multicentric phase IV study performed in three parallel groups.		
Number of patients	Planned for enrollment	:	N=60 (internal pilot phase to re-calculate the total sample size without unblinding)
	Enrolled and randomized	:	N=63 (two patients did not receive any study medication)
	Safety population/Full Analysis Set	:	N=61
	Per Protocol Set	:	N=52
Diagnosis and main criteria for inclusion	Male and female patients ≥ 18 and ≤ 80 years of age scheduled to undergo planned elective surgery of the pancreatic head (PPPD); ASA (American Society of Anesthesiology) class maximum III; heart failure not present or maximum NYHA (New York Heart Association) class II.		
Test product	Hyper-oncotic balanced HES 130/0.42 solution (Tetraspan® 10%)		
Dose	Dosing was performed in steps of bolus infusions of usually 250 mL/5 min according to a detailed algorithm by measuring stroke volume (SV) with esophageal doppler to achieve a target controlled preload optimum. After having reached the maximum dose of 30 ml/kg bw/d blinded treatment with crystalloid bolus infusions was continued until a maximum dose of 50 ml/kg/d (which is the maximum daily dose for the reference product Tetraspan 6%) was reached. Thereafter, open-label therapy with Sterofundin ISO using the algorithm until end of surgery was maintained. During surgery, a continuous basal crystalloid infusion of 4 mL/kg bodyweight (bw)/h was administered concomitantly.		
Mode of administration	intravenously (i.v.)		
Batch no.	9424H52, 0405H51		
Duration of treatment	After induction of anaesthesia and having obtained reliable SV measurements with the esophageal doppler until end of surgery.		
Reference product	Iso-oncotic balanced HES 130/0.42 solution (Tetraspan® 6%)		
Dose	Dosing was performed in steps of bolus infusions of usually 250 mL/5 min according to a detailed algorithm by measuring SV with esophageal doppler to achieve a target controlled preload optimum. When the dose of 50 ml/kg bw/d was reached, open-label therapy with Sterofundin ISO using the algorithm until end of surgery was maintained. During surgery, a continuous basal crystalloid infusion of 4 mL/kg bw/h was administered concomitantly.		
Mode of administration	i.v.		
Batch no.	9265H51, 0363H51		
Descriptive control	Balanced electrolyte solution (Sterofundin ISO)		
Dose	Dosing was performed in steps of bolus infusions of usually 250 mL/5 min according to a detailed algorithm by measuring SV with esophageal doppler to achieve a target controlled preload optimum. When the dose of 50 ml/kg bw/d was reached, open-label therapy with Sterofundin ISO using the algorithm until end of surgery was maintained. During surgery, a continuous basal crystalloid infusion of 4 mL/kg bw/h was administered concomitantly.		
Mode of administration	i.v.		
Batch no.	9395A244, 0356A241		

Criteria for evaluation	
Efficacy	A multiple ordered **primary endpoint** was chosen: 1st : Intraoperative required amount of HES (10%, 6%) [mL] 2nd : Time until fully on oral (solid) diet [days].
Efficacy	**Secondary endpoints** Hemodynamics ○ Systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean (MAP), heart rate (HR), central venous pressure (CVP) ○ Cardiac index (CI), SV, systemic vascular resistance (SVR) using esophageal Doppler and PiCCO ○ cumulative dose of norepinephrine ○ Intrathoracic blood volume index (ITBVI) and extravascular lung water index (EVLWI) (PiCCO) Concomitant medication / therapy ○ open label Sterofundin ISO during surgery within volume algorithm ○ basal fluid administration Ventilatory support Nursing Delirium Screening Scale (NuDesc) Gastrointestinal parameters ○ time until bowel movements (on auscultation) ○ time to first flatus ○ time to first defecation ○ intraabdominal pressure Injury scores (sequential organ failure assessment score (SOFA), simplified acute physiology score (SAPS II), acute physiology and chronic health evaluation-score (APACHE II)) Length of stay in intensive care unit (ICU) / intermediate care unit (IMCU) (fulfillment of ICU / IMCU release criteria according to the Aldrete score, Aldrete 1995) Time until criteria for 'fit for discharge from hospital' are fulfilled (hospitalization release criteria according to Marshall et al., 1999, Marshall and Chung, 1997) Complication rate (after ICU discharge) – surgical complications such as re-do surgery (e.g. anastomotic insufficiency), disturbed wound-healing or medical complications Health Related Quality of Life (HRQoL) according to the EQ-5D questionnaire

Safety	Hemodynamics ○ SAP, DAP, MAP, HR, CVP ○ CI, SV, SVR using esophageal Doppler and PiCCO ○ cumulative dose of norepinephrine ○ ITBVI and EVLWI (PiCCO) Blood gas analysis (partial pressure of carbon dioxide (pCO_2), partial pressure of oxygen (pO_2), hydrogen carbonate (HCO_3), arterial oxygen saturation (SaO_2)) Hemoglobin, hematocrit, electrolytes (Natrium, Potassium, Calcium, Chloride) Cardiac function (troponin or high-sensitivity troponin, brain natriuretic peptide (BNP) or N-terminal pro brain natriuretic peptide (NT-pro-BNP)) Acid-base status (pH, base excess, lactate) Inflammatory reaction ○ facultative Interleukin (IL) 6, IL10, IL6 / IL10-ratio ○ plasma clotting time (PCT), C-reactive protein (CRP) ○ Systemic inflammatory response syndrome (SIRS) Renal function ○ diuresis / urinary output ○ serum: creatinine, Blood urea nitrogen (BUN), urea, Haemoglobin A1c ($HbA1_c$) ○ urine: creatinine, α_1-microglobulin, α_1-microglobulin / creatinine-ratio, *N*-Acetyl-*β*-Glucosaminidase (ß-NAG) ○ Glomerular filtration rate (GFR) (Crockcroft and Gault, MDRD (Modification of diet in renal disease)) Hemostasis ○ Prothrombin time (PT), activated partial thromboplastin time (aPTT), Fibrinogen ○ von Willebrand factor-antigen (vWF-Ag), vWF-Ristocetin-Cofactor (vWF-RiCo) ○ Factor VIII plasma activity (FVIII:c) ○ ROTEM: Clotting time (CT), Clot formation time (CFT), Maximum Clot Firmness (MCF); using ExTEM and FibTEM PONV (post-operative nausea and vomiting) (Serious) Adverse Events
Statistical methods	Descriptive statistics Mann-Whitney U test (2-group comparison) Kruskal-Wallis test (3-group comparison) t-test (2-group comparison) F test (3-group comparison; ANOVA) Wilcoxon test Logistic regression analysis χ^2 test Pearson partial correlation coefficient controlled for treatment Spearman partial correlation coefficient controlled for treatment Kaplan-Meier plot, logrank test Significance level α=0.05 two-tailed Significance level of backward elimination in logistic regression analyses α=0.15.

MAIN RESULTS

The study was designed with an internal pilot phase to evaluate in a blinded manner the pooled variances of the primary variables of the HES-groups in order to re-evaluate sample size calculation. This blinded assessment of the pooled variances after recruitment of in total 63 patients showed that the variances were much larger than initially assumed leading to much higher sample sizes than initially estimated. Finally, it was decided to terminate the study in accordance with the study protocol. Thus, the data analysis of the pilot phase are presented in the following.

Efficacy results

- **Amount of HES administration in the Full Analysis Set (FAS)**

Parameter	Est	T10%	T6%	HES	S ISO	TT	10%	6%	H
FAS, double-blind trial medication [mL]	mean SD	2041.7 862.8	2215.9 787.9	2137.5 816.4	2726.2 1024.4	–	○	○	○
FAS, double-blind HES solution [mL]	mean SD	1694.4 621.6	2170.5 799.5			–			
FAS, double-blind trial medication [mL/kg]	mean SD	27.25 12.49	33.05 11.85	30.44 12.33	37.35 13.94	–	●	–	○
FAS, double-blind HES solution [mL/kg]	mean SD	21.93 6.99	32.24 11.62			●			

TT = Tetraspan 10% vs. Tetraspan 6%
10% = Tetraspan 10% vs. Sterofundin ISO
6% = Tetraspan 6% vs. Sterofundin ISO
H = HES vs. Sterofundin ISO

– = not significant
○ = significant 5% level
● = significant 1% level

A lower amount of HES solution in mL was administered via Tetraspan 10% compared with Tetraspan 6% which was not significant.

However, there were several statistically significant ($p < 0.05$) differences between the study groups at baseline, e.g. body weight, duration since last fluid intake, pre-operative pCO_2, circulating blood volume in males). Thus, when relating the amount to the individual body weight of the patient, the amount (mL/kg bw) of Tetraspan 10% was significantly less compared to Tetraspan 6%.

A significant higher amount of fluid replacement was administered in the Sterofundin ISO group.

The comparisons Tetraspan 10% vs. Tetraspan 6% are well confirmed in the Per Protocol (PP) population. In the PP population, the comparisons HES vs. Sterofundin ISO were equidirectional but less pronounced than in the FAS.

- **Time until fully on oral (solid) diet in the FAS**

  The median time until fully on oral (solid) diet was

  - Tetraspan 10% : 7.9 days
  - Tetraspan 6% : 7.9 days
  - Sterofundin ISO: 7.8 days.

  The group differences were not significant.

- **Other Efficacy Variables**

  For the following hemodynamic variables differences between groups were observed:

  - CI: CardioQ: The CI increased in both Tetraspan groups by 1.1 ± 1.0 and 1.1 ± 0.9 L/min/m^2, respectively. Upon Sterofundin ISO a smaller increase of CI was observed, resulting in statistically marked differences versus Tetraspan 10% (p=0.0757) and Tetraspan 6% (p=0.0846). The difference between the pooled HES group and Sterofundin ISO was significant (p=0.0406).
  - SV: CardioQ: The SV increased in both Tetraspan study groups, but not in the Sterofundin ISO group. Therefore, all three comparisons vs. Sterofundin ISO (Tetraspan 10% p=0.0009; Tetraspan 6% p=0.0102; HES p=0.0006) were statistically significant. A higher increase in SV upon Tetraspan 10% compared with Tetraspan 6% was statistically not significant (p=0.3236).

  No differences between groups were noted for other secondary efficacy variables.

Safety results

- **Adverse events (AEs)**

  The following incidences of AEs were observed:

First occurrence of event	Tetraspan 10% [N=18]	Tetraspan 6% [N=22]	Sterofundin ISO [N=21]	χ^2 test (p-value)
Before start of study medication	5 (27.8%)	8 (36.4%)	5 (23.8%)	0.6535
After start of study medication before start of surgery	1 (5.6%)	2 (9.1%)	–	0.3827
During surgery	9 (50.0%)	8 (36.4%)	12 (57.1%)	0.3825
After surgery before admission to ICU*	2 (11.1%)	2 (9.1%)	2 (9.5%)	0.9758
After admission to ICU	[N=15] 13 (86.7%)	[N=19] 15 (78.9%)	[N=20] 15 (75.0%)	0.6950
Summary: during or after surgery (incl. ICU)	16 (88.9%)	17 (77.3%)	19 (90.5%)	0.4151

[*: incl. post-surgery period in patients not submitted to ICU]

Regarding the summary, the most common System Organ Classes (SOCs) were

- ○ Inv Investigations : N=38
- ○ Vasc Vascular disorders) : N=21
- ○ Genrl General disorders and administration site conditions : N=19
- ○ Inj&P Injury, poisoning and procedural complications : N=19
- ○ Resp Respiratory, thoracic and mediastinal disorders : N=19
- ○ Metab Metabolism and nutrition disorders : N=17
- ○ Blood Blood and lymphatic system disorders : N=13
- ○ Surg Surgical and medical procedures : N=11
- ○ Gastr Gastrointestinal disorders : N= 9
- ○ Infec Infections and infestations : N= 8
- ○ Nerv Nervous system disorders : N= 6
- ○ Psych Psychiatric disorders : N= 5

(further incidences < 5).

No statistically significant differences between the study groups were detected in all and on the level of SOCs.

Altogether, during and after surgery (including ICU) 40 AEs occurred in 16 patients of the Tetraspan 10% group, 43 AEs in 17 patients of the Tetraspan 6% group and 50 AEs in 19 patients of the Sterofundin ISO group. Comparison of AE incidences in the study groups revealed no differences:

MedDRA SOC		Tetraspan 10% [N=18]	Tetraspan 6% [N=22]	Sterofundin ISO [N=21]	χ^2 test (p-value)
Any patient with AE		16 (88.9%)	17 (77.3%)	19 (90.5%)	0.4151
Blood	Blood and lymphatic system disorders	3 (16.7%)	3 (13.6%)	7 (33.3%)	0.2449
Card	Cardiac disorders	1 (5.6%)	1 (4.5%)	2 (9.5%)	0.7880
Gastr	Gastrointestinal disorders	4 (22.2%)	2 (9.1%)	3 (14.3%)	0.5059
Genrl	General disorders and administration site conditions	7 (38.9%)	7 (31.8%)	5 (23.8%)	0.5960
Hepat	Hepatobiliary disorders	1 (5.6%)	2 (9.1%)	1 (4.8%)	0.8309
Immun	Immune system disorders	1 (5.6%)	1 (4.5%)	–	0.5719
Infec	Infections and infestations	3 (16.7%)	2 (9.1%)	3 (14.3%)	0.7645
Inj&P	Injury, poisoning and procedural complications	5 (27.8%)	7 (31.8%)	7 (33.3%)	0.9293
Inv	Investigations	12 (66.7%)	12 (54.5%)	14 (66.7%)	0.6441
Metab	Metabolism and nutrition disorders	3 (16.7%)	6 (27.3%)	8 (38.1%)	0.3296

- **Adverse drug reactions (ADRs)**

During or after surgery (including ICU) 4 ADRs were observed in 4 patients. The following incidences of ADRs were observed without differences between groups:

MedDRA SOC		Tetraspan 10% [N=18]	Tetraspan 6% [N=22]	Sterofundin ISO [N=21]	χ^2 test (p-value)
Any patient with ADR		2 (11.1%)	1 (4.5%)	1 (4.8%)	0.6489
Genrl	General disorders and administration site conditions	–	1 (4.5%)	–	0.4061
Inv	Investigations	1 (5.6%)	–	1 (4.8%)	0.5527
Vasc	Vascular disorders	1 (5.6%)	–	–	0.2969

ADRs – none of them were serious – were leg edema (Tetraspan 6%), hypotension (Tetraspan 10%) and quick value decreased (Tetraspan 10%, Sterofundin ISO). All ADRs were resolved.

- **Serious adverse events (SAEs)**

  In total, 10 patients experienced at least one SAE.

  - Tetraspan 10% : N=2 (11.1%)
  - Tetraspan 6% : N=5 (22.7%)
  - Sterofundin ISO: N=3 (14.3%; including one death).

Altogether, 14 SAEs (Hepatobiliary disorders; Immune system disorders; Injury, poisoning and procedural complications; Psychiatric disorders; Cardiac disorders; Gastrointestinal disorders; Respiratory, thoracic and mediastinal disorders) were observed.

The relationship to the study medication was rated unlikely in all cases.

Conclusions

Although the study was terminated already after the pilot phase only, there is a trend revealing that less Tetraspan 10% than Tetraspan 6% was administered. The amount of HES solution administered during surgery was

- Tetraspan 10% : 1694.4 ± 621.6 mL
- Tetraspan 6% : 2170.5 ± 799.5 mL.

The treatment difference was not statistically significant (p=0.1114). Besides early termination of the study, this result might also be caused by a marked inhomogeneity of body weight in male patients (p=0.0012). If the HES doses were related to body weight, the treatment difference was significant (p=0.0024):

- Tetraspan 10% : 21.93 ± 6.99 mL/kg
- Tetraspan 6% : 32.24 ± 11.62 mL/kg.

The relation 32.24:21.93 = 147% represents very well the volume effect of the hyper-oncotic Tetraspan 10%.

Noteworthy that a significantly higher amount of the crystalloid Sterofundin ISO was administered in comparison to HES, although this group served as descriptive control only.

Drug related adverse events (adverse drug reactions) which were neither serious nor unexpected occurred in 4 patients only (Tetraspan 10% 2 patient, Tetraspan 6% and Sterofundin ISO each 1 patient).

The intraoperatively hemodynamic stabilisation was achieved better with HES as indicated by the statistically significantly increased stroke volume resulting in statistically significant less amount of HES needed compared to Sterofundin ISO. This result went along with no safety concerns in the three groups.